NICE and the challenge of cancer drugs

NICE has introduced new criteria for appraising end of life treatments. **James Raftery** looks at how they might affect availability by applying them to previously refused drugs

New drugs for cancer are posing problems for the United Kingdom's National Institute for Health and Clinical Excellence (NICE) and similar agencies internationally. The high price of these drugs is not always accompanied by commensurate improvements in health,[1] and their cost effectiveness (usually measured as cost per quality adjusted life year (QALY)) is consequently poor. The decisions to allow NHS use of trastuzumab (Herceptin) and imatinib (Glivec) pushed NICE's cost effectiveness threshold above its notional £30 000 (€34 000; $46 000) per QALY.[2] These decisions took place against a background of legal action by patients, attendant publicity, and political discomfort.

In the second half of last year NICE provisionally rejected six cancer drugs on grounds of their high cost per QALY. When it became clear that patients who wished to purchase these drugs privately would be denied free NHS care, a political crisis became likely.[3] This prompted the Richards review,[4] which recommended that patients who purchased unapproved drugs should remain eligible for free NHS care and also recommended that NICE should review its cost effectiveness threshold for end of life drugs.

After a brief consultation NICE outlined a new approach to end of life drugs to apply from January 2009. To qualify for the new approach drugs must meet specific criteria: small patient population, short life expectancy (normally less than two years), extension of life expectancy (normally at least three months), and no alternative treatment with comparable benefits available through the NHS.[5] Here I examine the effect the new arrangements would have had on all cancer drugs that NICE has refused or proposed to refuse because of poor cost effectiveness.

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Cancer drugs refused by NICE, with proposed criteria for end of life drugs and NICE's estimates of cost and cost per QALY[7]

Drug	Condition (prognosis where available)	Survival gain	Comparison*	Cost per patient (£)	NICE (manufacturer) estimated cost /QALY (£000)
Final guidance					
Bevacizumab (1st line)	Colorectal cancer (metastatic, 12% 5 year survival	4.7 months	Bevacizumab+interferon *v* interferon	17	63 (88)
Cetuximab (2nd line)		2.6 months TTP	Cetuximab+irinotecan *v* best supportive care	12	>30 (33)
Pemetrexed	Lung cancer (non-small cell, locally advanced or metastatic)	None	Docetaxel or best supportive care	18	60 (19)
Fludarabine (1st line)	Leukaemia lymphocytic	PFS 31% *v* 23% at 3 years	Chlorambucil	5	>30 (26)
Provisional guidance					
Bevacizumab	Renal cancer (advanced or metastatic, 12% 5 year survival)	5 months PFS	Bevacizumab+interferon *v* interferon	40	171 (75)
Sunitinib		6 months PFS	Interferon	31	72 (29)
Sorafenib		3.3 months PFS	Best supportive care	23	103 (91)
Temsirolimus		3.6 months	Interferon	18	94 (102)
Lenalidomide	Multiple myeloid leukaemia	1.8 months	Lenalidomide *v* dexamethasone; lenalidomide+dexamethasone *v* dexamethasone	44	47-69 (47)
Lapatinib	Breast cancer (advanced metastatic)	9.5 weeks PFS	Laptinib+capecitabine *v* capecitabine	20	70-94 (81)
Cetuximab (1st line)	Colorectal cancer (metastatic, 12% 5 year survival)	0.5 week PFS	Cetuximab *v* FOLFOX (calcium folinate, flurouracil+oxaliplatin)	23	>30 (63)

PFS= progression free survival, TTP=time to progression.
*Comparison used to estimate QALY.

Effect of NICE criteria

I examined all NICE's current technology appraisals from 1999 to November 2008, both those concluded and in consultation, to identify cancer topics. I then extracted information relevant to the proposed new criteria, specifically the prognosis of the disease, the gain in life expectancy from treatment, and the comparison on which this was based. The existence of a comparator indicates an alternative treatment of comparable benefit was available in the NHS. Given the imprecision of the criterion "small patient populations" and lack of data, I have not considered this criterion.

NICE appraised 42 cancer interventions during 1999-2008. Of these, 22 were recommended for use with no or minor restrictions, 13 had major restrictions imposed, and seven were not recommended. It also issued provisional guidance on a further seven cancer drugs, all of which were not recommended. The reason for not recommending the 14 drugs was poor cost effectiveness in 11 cases and lack of evidence in the others.

The prices of the 11 drugs refused on grounds of cost effectiveness were high, particularly for those it provisionally refused (table). These drugs included the five most costly that NICE has ever appraised. NICE's estimate of the cost per QALY was well above the £30 000 threshold. Most of the company submissions, which normally purport to show their drug has a cost effectiveness below the threshold,[6] also gave much higher costs per QALY.

Although data were often lacking on the extent to which these drugs would meet NICE's proposed criteria for end of life drugs, most would fail to meet the criterion that no alternative treatment with comparable benefits existed. If best supportive care is taken to indicate the lack of any alternative treatment, only two drugs would qualify (sorafenib for renal cancer and lapatinib for breast cancer). One, cetuximab, was compared in combination with irinotecan to best supportive care. The eight other rejected drugs were compared with other drugs, often as add-ons.

Data on prognosis untreated were either absent or in a form not readily expressed in terms of average life expectancy. Although data on the expected survival gains from treatment were available for three drugs, the gains for the others were usually expressed in terms of progression free survival or time to progress, neither of which can be readily expressed in terms of absolute survival.

Further difficulties ahead

My analysis suggests that NICE's new arrangements for appraising end of life drugs may do little to improve availability of expensive cancer treatments. Few of the rejected drugs would qualify under the new criteria, with much depending on the interpretation of the criterion that no alternative treatment with comparable benefit is available through the NHS.

The main attraction of the cost per QALY measure is its universal applicability. Making an exception for any group—such as, life extending treatments for terminally ill patients—limits that universality and sets a precedent for other groups. In addition, setting the threshold higher for some groups within a fixed overall budget results in other patient groups being denied treatment.

NICE guidance against NHS use of cancer drugs is controversial when those drugs offer any prospect of increased life expectancy. Patients inevitably protest when an estimated average cost per QALY is used to deny them treatment. This valuing of what is essentially a statistical or abstract life is challenged by real patients, who attract publicity. Ethical, legal, and political dilemmas become high profile stories. From this perspective NICE can be seen as having responded to public concern.

More generally, decisions by companies to set prices that lead to high cost per QALY values constitute a direct challenge to NICE's use of the measure. NICE celebrates its 10th birthday in 2009 having had to make a major change in its methods. Its attempt to minimise the effects of these changes will no doubt be tested in future appeals against its findings.

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