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Editorial Comment

Being NICE is not the problem!

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Access to new treatments for cancer is a matter of money. Without third party payment most patients cannot afford the new medicines. Decisions by agencies such as NICE must therefore be critically reviewed and debated. Mason and Drummond's study in this issue[1] provides an important insight into NICE's decisions on cancer drugs. They conclude that the rejection rate has increased over time, and relate this to the change in the appraisal methods in August 2006, and to changing evidence on cost-effectiveness.

The Single Technology Appraisal (STA) process was introduced to solve the problem with NICE's blight; that no decision is a negative decision. A consequence is that appraisals are done earlier on more uncertain data, which may have contributed to the higher rejection rate. However, this must then be weighted against the positive appraisals that otherwise should have been delayed.

During the first period, until June 2006, a negative decision was driven by absence of data on effectiveness, while in the second period, the price is judged as too high in relation to estimated effectiveness. Focus has thus shifted from effectiveness to the price of the drug, which is not without complications, since there is only one price but several assessments of effectiveness. Cost-effectiveness is not specifically related to the drug, but is also dependent on the patient population for which it is used, and the alternatives considered. Cancer drug development is a process where the drug is first tried in small patient populations with incurable disease, and then extended to larger patient populations and more indications including curative adjuvant treatment. Trastuzumab, as with several other breast cancer drugs, is more cost-effective in early adjuvant treatment than in metastatic disease, which was the first licensed indication.

Cost-effectiveness can vary over time in unplanned directions. Bevacizumab has been developed for several cancer types, and sub-populations, and it would be surprising if with a single price, there would not be differences in cost-effectiveness. The developer may initially try to go for the indications with highest unmet needs, which would predict that cost-effectiveness will decline as further indications are added. However, it is not easy to predict effectiveness, and the development process has a number of other restrictions. We would thus expect a certain variation over time in cost-effectiveness for a specific drug as it is developed. Value for money for the drug is different from the value in different indications and important when we consider optimal incentives for innovation.

The new focus on price is probably a factor behind the recently published supplementary advice for the Appraisal Committees, to be taken into account 'when appraising treatments which may be life-extending for patients with short life expectancy, and which are licensed for indications affecting a small number of patients with incurable illnesses'.[2] Cancer is not explicitly mentioned, but the new rules apply to a number of up-coming appraisals of cancer drugs. In essence, a higher price or cost per QALY is accepted because NICE should take 'account of its responsibility to recognise the potential for long term benefits to the NHS of innovation'. This is a welcome change, but it is difficult to see the logic

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that it is restricted to specific indications for small patient populations. The new advice does not address the basic problem of lack of information at launch of a new drug or indication, and the variations in cost-effectiveness between indications and over time, but may be seen as a first step towards a more comprehensive and long term approach.

NICE is important only if the decisions have an impact on how patients are treated in clinical practice. This may seem self evident, since NICE gives guidance for resource allocation in the NHS. However, since the consequences and policy implications of the findings by Mason and Drummond are dependent on the impact on patient access to treatment, there is reason to take a closer look at the evidence.

Jönsson and Wilking have, in a number of studies, documented the slow and low uptake of new cancer drugs in the UK compared to other European countries. A new study[3] shows that the situation has not improved, but rather the opposite (Fig. 1); the use of cancer drugs in the UK is about one third of that in France, and half of that in other comparable European countries (E13 in Fig. 1), including Germany, Italy, and Spain. The use is lower not only for new drugs, but also for established drugs, in the figure represented by those drugs first marketed in 1998 or earlier. The very low sales for drugs first marketed after 2002 seems to confirm the conclusion by Mason and Drummond that the relative position has worsened during the last few years.

However, the impact of NICE is unclear. Analysis of a subgroup of well established cancer drugs introduced in 2002 or earlier shows that the UK only has two-thirds of the use of that in Germany, Italy and Spain, and 40% of that in France. This group of drugs has a positive NICE appraisal and accounts for about half of all sales of cancer drugs. The patterns are the same for all drugs, with the exception of two breast cancer drugs where the use is closer to the European average. One is aromatase inhibitors, where the use of a UK produced brand is particularly high, and the second is trastuzumab, as shown in Fig. 2. Note that the two NICE appraisals of trastuzumab in March 2002 and August 2006 show no effect on use. The first appraisal did not affect uptake and the second came after trastuzumab use had already increased. This increase came in the autumn of 2005 and was probably linked to the media debate in the UK about NICE's blight.

The conclusions must then be that the main problem with NICE is that it does not fulfil the intended role to direct NHS expenditures to technologies with proven effectiveness and cost-effectiveness. While there are 56 assessments for 24 different drugs, there are not yet systematic assessments on how resources are spent on cancer in the UK, and no mechanisms to reallocate funds to improve cost-effectiveness. The usual explanation given is that it is not possible to force the clinicians to prescribe the new drugs. But clinical judgement may mask specific treatment patterns that can be revealed through systematic studies. Is treatment available for those patients that can benefit most, or are there specific groups of patients that are excluded from treatment? NICE was instituted to eliminate irrelevant factors for access to therapy ('post-code prescribing'), and should thus be evaluated according to these criteria as well, as Mason and Drummond also point out.

NICE's focus on cancer drugs is surprising, considering that they account for less than 1% of NHS spending. However, what is even more surprising is that there seems to be no link between the appraisals and the actual spending on cancer and cancer drugs. The absolute number of negative appraisals is small, but it is not possible to detect any effect of the positive appraisals.

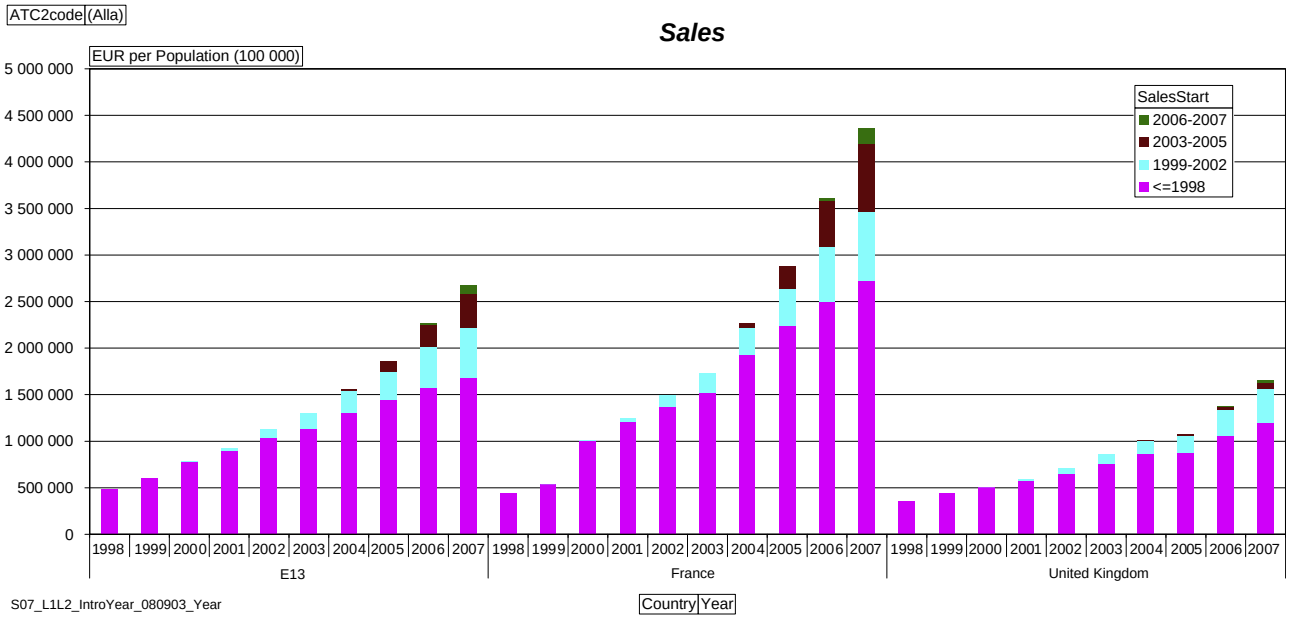

Fig. 1 – Sales of cancer drugs in 1998–2007 in E13, France and the UK in Euros (€)/100,000 inhabitants. Sales distributed after the period of first introduction (vintage) of the drug.

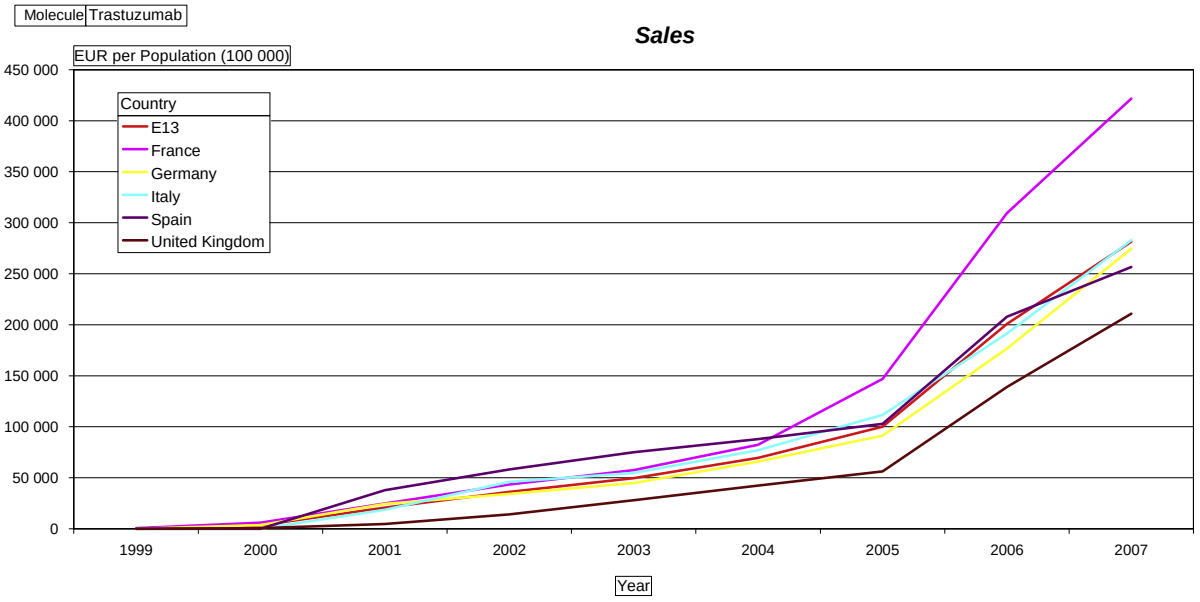

Fig. 2 – The usage of trastuzumab expressed as mg/case (related to mortality in breast cancer in 2003) in E13, France, Germany, Italy, Spain and the UK. The first NICE appraisal was in 2002 and the second in 2006; neither seems to have any impact on uptake. In 2005, the Minister of Health authorised the use of trastuzumab for adjuvant treatment.

Delayed introduction and use of new therapies may save money if it later turns out that they are ineffective or unsafe, and should not be used. However, the other side of the coin is that this increases the risk of not using clinically effective, as well as cost-effective, therapies. It is not easy to strike the right balance. However, it is surprising that the UK, which is so prominent in Europe in medical research, and where the public voluntarily contributes most per capita in the world to cancer research, is so passive in the continued evaluation of new cancer drugs when they have reached the market. Cancer research does not end with market authorisation, and it is impossible to have all relevant information for assessment of cost-effectiveness at that time. We need well designed follow-up studies of new cancer drugs, and flexible decision-making about funding, to strike the right balance between being nice and nasty.

Conflict of interest statement

None declared.

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