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Friday 7th April 2006

Emily Marschke
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BY E-MAIL

Dear Emily,

HEALTH TECHNOLOGY APPRAISAL – Bevacizumab and cetuximab for the treatment of colorectal cancer

Thank you for providing us with a copy of the Assessment Report for the above technology appraisal and for extending to us the opportunity to comment on the document.

Our comments on the technical content of the report are set out below.

KEY ISSUES

Survival extrapolation approach

The economic model submitted by Roche and that developed by ScHARR differ primarily with regard to the approaches taken to estimating survival. The Assessment Report outlines the Roche economic modelling approach in Sections 6.1.3.2 and 6.1.3.8, and then describes the ScHARR approach in comparison to the Roche approach in Sections 6.2.1.1, 6.2.1.4.1, 6.2.3.2, 6.2.3.3 and 6.2.3.4.1.

Whereas the ScHARR model uses empirical overall survival and progression free data as the basis for extrapolations of mean duration in pre-progression and post-progression health states, the Roche model uses the empirical progression-free survival data as well as data on post progression to death as the basis for extrapolation.

As a result of utilising these alternative approaches, the estimates of cost-effectiveness differ. In Sections 6.1.3.8 and 6.2.3.4.1 it is argued that for study AVF2107 the Roche estimate is conservative (compared to the ScHARR result) and for study AVF2192 the Roche estimate is optimistic (again, compared to the ScHARR result).

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Having undertaken close analysis and scrutiny of both approaches and also taken expert independent advice, Roche considers both approaches to be valid but each with relative advantages and disadvantages.

However on this occasion, having given due consideration to both approaches Roche endorses ScHARR's approach to estimating survival and subsequent economic results.

Discussion of alternative approaches

The ScHARR method of using overall survival is the most 'direct' in the sense that this approach requires fewer steps to develop an estimate of life years gained. However, this apparent advantage may be offset when it is considered that the model needs to estimate both duration of progression-free survival and post-progression survival health states in order to calculate quality-adjusted life years gained.

The Roche method of using post progression survival as its basis avoids the potential contradiction that treatment with bevacizumab is detrimental to survival post progression. This contradiction is implied in the ScHARR overall survival based model for study AVF2192, which estimates that the mean time after progression is lower in the bevacizumab cohort, and reduces a progression-free survival gain of 3.93 months to an overall survival gain of 2.22 months.

The trial publication on study AVF2192 makes clear that inbalances in baseline patient characteristics between the two arms of the trial may have confounded overall survival comparisons, partly due to the small sample size. For example patients in the treatment arm were under represented in terms of serum albumin <3.5 g/dL, a baseline characteristic for which treatment was associated with a hazard ratio for death of 0.46 (0.29-0.74). Overall survival may therefore be a problematic measure of treatment effect, in this study.

Additionally a greater proportion of patients in the AVF2192 control arm received oxaliplatin or irinotecan as second line therapy than did patients in the treatment arm.

The Roche approach of employing a proportional hazard for post progression survival constrains post progression mortality hazards to be equal. This removes any bias due to second line therapy in the trial, and mitigates (though does not remove) the effect of imbalance in randomised patients' characteristics that were important for overall survival.

For study AVF2192 a sensitivity analysis where survival is kept identical after progression in both arms would therefore be an appropriate avenue for further analysis.

DETAILED POINTS OF FEEDBACK

Bullet point 1, Section 2.6 (p 8) and bullet point 1 Section 9.2 (p147)

Retrospective analysis of evidence from pivotal study AVF2107 suggested that continuation of bevacizumab after disease progression has no impact on disease outcome. Although this conclusion was based on uncontrolled data extracted retrospectively, it did not provide an attractive hypothesis for testing in future trials. Therefore, it is unlikely that further research will be undertaken in this area.

Bullet point 5, Section 2.6 (p8) and bullet and bullet point 1 Section 9.4 (p149)

The absence of a randomised phase III study demonstrating the benefit of irinotecan plus cetuximab versus standard of care in irinotecan-refractory colorectal cancer is rightly pointed out as a problem, as is the problem of comparing irinotecan plus cetuximab with best supportive care. However, there is no reason why the combination should not be compared with 5-FU plus oxaliplatin in patients failing first-line treatment with irinotecan plus 5-FU/FA. This would be ethically acceptable and relevant to UK clinical practice where irinotecan plus 5-FU/FA is a NICE endorsed first-line option and oxaliplatin plus 5-FU/FA is NICE-endorsed as a second-line treatment.

Section 3.4 (p12 and 13)

The difficulty of obtaining accurate epidemiological data in this area is acknowledged. However, in an evolving field such as this, the use of figures almost a decade old is probably unwise. The authors acknowledge that published literature reports the percentage of patients diagnosed with colorectal cancer who have metastases at diagnosis as being in the range 20% to 55%. However, the 55% figure comes from a 1997 published paper, the figure of 20% from 2000 is much more plausible. The same 1997 paper is also used as the source of 5 year survival – quoted at 35% - when in fact more recent Office of National Statistics figures show the 5-year survival to be 47%[1].

Although the interventions being appraised in this review are specifically for use in metastatic disease, understanding their clinical and budget impact requires a good understanding of the broader picture – few patients with metastatic disease survive for 5 years. Therefore, it can be assumed that patients alive 5 years from diagnosis with colorectal cancer do not have metastatic disease and have not received or been candidates for either intervention. If such patients make up almost a half of colorectal cancer patients rather than one-third, the budget impact of interventions restricted to metastatic disease is significantly reduced

Figure 1 assumption I (p. 17)

The figure of 85-90% of patients with advanced colorectal cancer receiving cytotoxic chemotherapy seems very high. It is much higher than the estimates previously used by ScHARR (35% in its 2002 assessment of oral fluoropyrimidines)[2]. Although treatment rates have almost certainly risen over recent years it seems unlikely that they have, generally, reached 85-90%. The use of such a high figure, based on the opinion of a single clinician, is likely to inflate the budget impact of the proposed interventions substantially.

Section 3.4.2, para. 3 (p. 23)

This section states that patients refractory to irinotecan-based chemotherapy typically have no further active treatment options available. This is only true of patients who have also already received oxaliplatin. The most recent NICE guidance on the chemotherapy of metastatic colorectal cancer[3] recommends that irinotecan and oxaliplatin-based regimens be made available under the NHS for the first- and second-line treatment of metastatic colorectal cancer.

Section 5.2.3.2, para. 1 (p.46) and Section 9.1. para 2. (p.147)

The author's express reservations about the applicability of the results obtained with bevacizumab in clinical trials to UK clinical practice because trial recruits were, generally, younger than those patients diagnosed with colorectal cancer in clinical practice. However, as the reviewers point out, one of the qualifying factors in studyAVF2192g – in which bevacizumab was highly effective -was advanced age, resulting in an average patient age of over 70 years. Additionally, as shown in Fig 3. in our original submission, younger age did not appear to predict for greater benefit from bevacizumab in phase III study AVF2107g. Therefore, there is no reason to hypothesise that older patients will not benefit from the addition of bevacizumab to their chemotherapy to the same degree as younger ones.

We hope that this feedback will be helpful to the Appraisal Committee.

Please do not hesitate to contact us if we can provide any further clarification on the feedback provided.

Yours sincerely.

Paul Catchpole

References

1. http://www.cancerresearchuk.org/aboutcancer/statistics/ *Accessed 20.03.06*
2. http://www.nice.org.uk/pdf/Assessmentreport_Capecetabine_cancer.pdf. *Accessed 20.03.06*
3. http://www.nice.org.uk/pdf/TA93Guidance.pdf *Accessed 20.03.06*

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Dear Carole,

HEALTH TECHNOLOGY APPRAISAL – Bevacizumab and cetuximab for the treatment of Colorectal Cancer -

ROCHE AVASTIN REGISTRY PROGRAMME

The purpose of this letter is to inform you that Roche intends to make bevacizumab available to NHS colorectal patients through a new mechanism known as the Avastin Registry Programme (ARP).

The ARP is an audit based registry and includes within it arrangements for making payments to NHS Trusts to cover the administration costs of bevacizumab and other associated infusional drugs given with it as part of bevacizumab containing regimens.

The potential introduction of this programme into the NHS will potentially have an impact on the current technology appraisal of bevacizumab which we believe needs to be investigated and brought to the attention of the Appraisal Committee. The attachment accompanying this letter fully describes the ARP proposals.

We would like to request that should the Appraisal Committee endorse the use of bevacizumab in one or both of the indications presently being appraised then the resultant NICE guidance should recommend that NHS clinicians must register all patients to whom they wish to prescribe bevacizumab in accordance with NICE guidance on the Avastin Registry Programme.

We would like to request that the NICE Technical Team and / or ScHARR investigate the impact of the ARP on the current appraisal and on the evidence base presented within the Assessment Report.

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Impact on ScHARR Assessment Report Evidence Base

Bevacizumab plus IFL

We note that the ScHARR economic model for study AVF2107 reported in the Assessment Report estimates that the mean number of bevacizumab administrations per patient course is 18.2.

If the administration cost which is to be paid for each bevacizumab infusion through the Roche ARP is multiplied by the mean number of bevacizumab infusions of 18.2 and this total administration cost is deducted from the administration costs in the economic model then this will have an impact on the resulting cost / QALY.

We would like to request that the NICE Technical Team and / or ScHARR investigate the impact of this change on the cost / QALY of bevacizumab plus IFL.

Bevacizumab plus 5-FU/FA

We note that the ScHARR economic model for study AVF2192 reported in the Assessment Report estimates that the mean number of Avastin administrations per patient course is 15.3.

If the administration cost which is to be paid for each bevacizumab infusion through the Roche ARP is multiplied by the mean number of bevacizumab infusions of 15.3 and this total administration cost is deducted from the administration costs in the economic model then this will have an impact on the resulting cost / QALY.

We would like to request that the NICE Technical Team and / or ScHARR investigate the impact of this change on the cost / QALY of bevacizumab plus 5-FU/FA.

Conclusion

Roche believes that the cost / QALYs presented for bevacizumab must be considered alongside the unusually innovative nature of bevacizumab as the first and only antibody treatment against vascular endothelial growth factor (VEGF) which has been shown to be effective in slowing tumour growth and produce measurable tumour shrinkage, leading to improvements in time to progression and overall survival beyond what has been seen so far with traditional chemotherapy.

Please do not hesitate to contact me if I can provide any further information regarding the proposed ARP. Copies of this letter have gone to DH colleagues Simon Reeve, Mike Brownlee and Professor Mike Richards.

Yours sincerely.

Paul Catchpole