Erlotinib for the treatment of non-small cell lung cancer

Report from the Decision Support Unit in response to additional data submitted by Roche

10th January 2008

Part 1: A Sutton. Critique of the network meta-analysis of overall survival in relapsed NSCL supplied by Roche in Appendix 2 (Further evidence identified by Roche) of their appeal.

Part 2: J Tosh and A Wailloo. Comment on the cost of docetaxel drug administration used in the STA for erlotinib for NSCLC.

PART 1

STA– Erlotinib for non small cell lung cancer (NSCLC)

Critique of the network meta-analysis of overall survival in relapsed NSCL supplied by Roche in Appendix 2 (Further evidence identified by Roche) of their appeal.

9th Jan 2008

By Alex Sutton (Reader in Medical Statistics, University of Leicester) on behalf of the DSU

Background

In the original submission, since no head-to-head trial evidence of erlotinib v docetaxel was identified, no synthesis was conducted and no estimate of relative effectiveness was obtained.

In the original submission, one trial was claimed to be pivotal for the effectiveness of erlotinib v placebo and 11 trials of docetaxel (versus various comparators) were reviewed. The results of the erlotinib trial were compared informally with the 11 docetaxel trials.

A network meta-analysis presented in Appendix 2 of the appeal document. The justification for this was stated as "The publication of the INTEREST study illustrating equivalent efficacy between the EGFR inhibitor gefitinib and docetaxel has allowed a network meta-analysis of current relapsed NSCLC treatments options." (I do not believe this to be correct since a network analysis was possible before, there was even a previous (Cufer 2006) trial making the same comparison.) The erlotinib trial, 3 of the 11 docetaxel trials reviewed in the original submission, a further trial of Gefitinib v. placebo, plus a further new docetaxel trial (Douillard 2007) are included in this new network meta-analysis.

Several aspects of this network meta-analysis were unclear from the submitted manuscript so clarification was sought on a number of points. This resulted in further documents (a letter outlining specific responses to my queries and a more detailed report of the network meta-analysis) being supplied by Roche.

Below is a summary and critique of the analysis drawing on all of the documentation submitted.

Summary

The odds ratio for erlotinib compared to docetaxel for overall survival in relapsed NSCLC was estimated by the network meta-analysis to be 0.845 (0.600 to 1.150).

I critique the process and assumptions made in the analysis which obtained this estimate below.

Critique

Inclusion criteria: The inclusion criteria for this network meta-analysis were transparent and defined in A2 of the clarification letter.

With respect to the interventions considered the letter states "The interventions were selected as those currently licensed in the UK for second-line treatment of NSCLC." These treatments are docetaxel, erlotinib, gefitinib, pemetrexed or best supportive care/placebo. This explains why 8 of the docetaxel trials reviewed in the original submission were not included in the network meta-analysis (i.e. they did not use a currently licensed comparator).

Since comparators for STA appraisals do not have to be licensed, alternative MTC networks potentially could have been constructed using non-licensed comparators. It is impossible for me to say whether similar estimates of effect of erlotinib v docetaxel would have been obtained had a different network been constructed. Not being a clinical expert in the area, I cannot guess how many further trials would be potentially eligible for inclusion in the MTC if a larger network had been constructed. However, given 8 known docetaxel trials are excluded, this does suggest considerable numbers of further trials may exist to populate an extended network, including non-licensed comparators (although, of course conducting such an analysis may have a large resource implication).

Search strategy: Full details were supplied in section A1 of Roche's clarification letter and this search strategy appears to be extensive and appropriate.

Statistical model: Full details of the statistical model(s) used in the synthesis were supplied. These include fixed and random effect Bayesain network meta-analysis models. Both of these look reasonable, but I am unclear which one was used to obtain the estimates in the reported analysis. The initial report said it was a random effect analysis, but the response to A7 of the clarifications suggests there was problems fitting the random effect model ("There are insufficient data available to allow a random effects variance to be reliably estimated") implying results must be from the fixed effect model? This specific issue is (still) unclear to me.

Comparability of the trials synthesised in network meta-analysis: I have very little clinical knowledge in this area, so am not qualified to full assess whether it is sensible to combine the six trials in the network meta-analysis. Details regarding characteristics of

the included trials, including details defining the patient populations are supplied in Tables 1 and 2 of the Roche report “Evidence synthesis to support Erlotinib in NSCLC”.

Summary:

I consider the responses made by Roche to provide clarification on most aspects of the MTC analysis. I am left unclear on 2 points. The first is the use of fixed or random effects analyses. The second, which I believe is the more fundamental issue, relates to defining the MTC network. Only licensed treatment regimes were included. Potentially, inclusion of further (unlicensed) treatment regimes may have allowed further trial evidence to contribute to the analysis. Without conducting such an analysis it is difficult to suggest how this would affect the estimate of relative effectiveness of erlotinib v docetaxel..

PART 2

COMMENT ON THE COST OF DOCETAXEL DRUG ADMINISTRATION USED IN THE STA FOR ERLOTINIB FOR NSCLC.

DECISION SUPPORT UNIT

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The cost of docetaxel administration used in the original submission was £125, and assumed to be an outpatient follow-up attendance with no treatment costs included (HRG: 370, NHS Reference Cost 2004). Using the most up to date NHS Reference Cost data (HRG: 370F, 2006) this cost has fallen to £123. However, the revised model submitted by Roche has assumed the cost of administration to be £299, assuming docetaxel is administered as a day case attendance (HRG: D98, NHS Reference Cost 2006). For a summary of the values, see Table 1 at the end of this report.

In considering the appropriate cost for the administration of docetaxel it is important to recognise that cost-effectiveness analyses should consider the value of the resources used in any procedure. Docetaxel is administered as an infusion lasting approximately one hour.

Roche have argued that the revision from an out patient cost to a day case cost is appropriate based on two points (page 18);

1. consistent with previous appraisal committee selections
2. the most appropriate source of data

Firstly, Roche compare docetaxel administration for NSCLC to rituximab for follicular lymphoma. They argue that the decision by the ERG and AC to assume a day case administration for rituximab justifies the use of a day case cost for docetaxel. However, rituximab is a therapy which requires an infusion lasting several hours. For example, in the STA of ritxumab for RA, the manufacturer (Roche) assumes that the average time taken to administer rituximab is 5 hours. Indeed, for the first infusion with rituximab, an overnight stay is not uncommon. Since docetaxel is administered over a much shorter time, it would be inconsistent to apply the same cost for docetaxel as has been used in the case of rituximab.

Secondly, the day case reference cost comprises all costs for patients treated within this HRG. This cost therefore includes a potentially wide range of treatments (lasting considerably longer than 1 hour) and their treatment costs. It would be expected that the average cost of this set of treatments could be substantially higher than the cost for the administration of docetaxel. In addition, the HRG includes all treatment costs for these patients. Since the actual cost of the drug is included as a separate component of the cost effectiveness model there is a risk of double counting if this cost is applied.

Thirdly, NHS outpatient visits are intended to cover short procedures which involve a doctor and where a bed may be required due to the active intervention and not the patient's condition. The requirements for docetaxel administration would appear to be more consistent with this definition than that of a day case.

Therefore, given the relatively short duration of time associated with docetaxel administration the more appropriate reflection of resource use is given by an outpatient visit rather than a day case attendance.

Table 1: Alternative cost estimates for the administration of docetaxel

	Cost	***Reference Cost Year***	***HRG***	***Details***	***Comment***
Original Roche submission	£125	2004	370	Outpatient follow-up attendance – medical oncology	Attendance – no treatment
	£123	2006	370F	Outpatient adult follow up attendance – medical oncology (attendance without treatment)	Attendance – no treatment
Revised Roche submission	£299	2006	D98	Day Cases – Chemotherapy with a Respiratory System Primary Diagnosis	Treatment and attendance
	£266	2004	D98	Chemotherapy with a Respiratory System Primary Diagnosis	Treatment and attendance
NHS Tariff	£87	2007-08	370 (tariff)	Outpatient Adult follow-up attendance tariff	
NHS Tariff	None found		D98 (tariff)	Day Case – Chemotherapy with a respiratory system primary diagnosis	