Clinical specialist statement

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Kevin Harrington

Name of your organisation (if applicable): Royal Marsden Hospital

Are you: (tick all that apply)

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **Yes**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so what is your position in the organisation where appropriate, (e.g. policy officer, trustee, member etc.)?
- other (please specify)?

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

This application deals with consideration of the use of cetuximab in the treatment of patients with stage III and IV head and neck cancer (HNC). At present, the standard management of this disease falls into two broad categories: (i) radical surgical excision followed by post-operative radiotherapy or chemoradiotherapy (for high-risk disease – defined as positive resection margins, N2b disease or nodal disease with extracapsular spread); or (ii) radical chemoradiotherapy. In some circumstances, patients with unresected disease are treated with radical radiotherapy without concomitant chemotherapy. In most cases, these patients are unfit to receive concomitant chemotherapy by virtue of co-existing medical conditions (renal dysfunction, pre-existing neuropathy, deafness, tinnitus), poor performance status (ECOG 2 or greater) or age (>70 years). The standard of care for concomitant chemotherapy is single-agent cisplatin. No standard dose regimen is universally accepted, but most centres would accept a dose of 100 mg/m^2 delivered on 2 or 3 occasions during radiotherapy.

There are considerable differences between different practices across the UK, but most units would accept the broad principles outlined above. Most differences relate to the selection of initial treatment modality (surgery vs chemoradiotherapy), radiation dose fractionation (20 to 35 fractions over 4 to 7 weeks) and the means of delivery of cisplatin (40 mg/m^2 per week to 100 mg/m^2 every 3 weeks).

Cetuximab has been assessed in a specific clinical indication in a large randomised phase III study (Bonner et al 2006; 354: 567-78) in 424 patients with stage III and IV HNC. Patients received radical radiotherapy (without concomitant chemotherapy) with or without intravenous administration of cetuximab. Patients received radiotherapy according to one of three fractionation schedules: concomitant boost 56%; once-daily fractionation 26%; twice-daily fractionation 18%. The median durations of locoregional control were 24.4 months vs 14.9 months for the cetuximab and control arms,

respectively. The corresponding median overall survival values were 49 months and 29.3 months, respectively. The addition of cetuximab was associated with greater cutaneous toxicity but no accentuation of mucositis.

The potential advantage of this technology is the lack of the typical side-effects of cisplatin chemotherapy – but at the risk of troublesome skin-rash and a low incidence of acute infusion reaction.

Unfortunately, the randomised phase III trial outlined above was designed to answer a question that has now been largely superseded by the widespread adoption of radical chemoradiotherapy in patients with unresected stage III and IV HNC. Therefore, in the absence of a formal phase III report of this agent in patients treated with radical chemoradiotherapy, it is not possible to recommend adoption of this agent for most patients with this condition. Instead, for this group, radical chemoradiotherapy should remain the standard of care. Similarly, for patients who have undergone a radical surgical procedure with high-risk pathological features, the use of post-operative chemoradiotherapy remains the treatment of choice as demonstrated by the EORTC and RTOG studies (Bernier et al 2004, Cooper et al 2004). It would be unreasonable to extrapolate the data from the study by Bonner et al (2006) to support the use of radiotherapy and cetuximab in an adjuvant post-operative setting (either with or without chemotherapy). Consideration of this question will require data from formal phase III studies in a post-operative setting.

However, there are circumstances in which it would be reasonable to consider the use of cetuximab and radiotherapy in unresected stage III and IV HNC. I would recommend the following scenarios (with the attached caveats):
(1) Patients with renal dysfunction (GFR < 50 ml/min) that precludes the safe delivery of concomitant cisplatin. Under these circumstances, there are no clear data that carboplatin represents an equivalent replacement therapy. Therefore, it would appear reasonable to offer this group of patients the potential benefit of adding cetuximab to radiotherapy.
(2) Patients with pre-existing grade 2 or greater peripheral neuropathy. In these patients the use of cisplatin is contra-indicated.
(3) Patients with ECOG performance score 2 or greater. However, it must be recognised that the study by Bonner et al (2006) involved few patients with poor (Karnofsky 60%, 70%) performance status (11% in radiotherapy alone arm, 10% in radiotherapy plus cetuximab arm). Therefore, it would be difficult to make a definitive statement in this regard. Nonetheless, it would seem reasonable to recommend the use of cetuximab in this group of patients.
(4) Patients aged 70 years or more. This consideration is based on data presented by Bourhis et al (ASCO 2006) demonstrating a reduced benefit from concomitant chemoradiotherapy in this group of patients. However, it must be borne in mind that the median ages in the study by Bonner et al (2006) were 58 years and 56 years in the radiotherapy alone and radiotherapy plus cetuximab arms, respectively. Therefore, in the absence of specific data on the subset of patients aged 70 years or older (likely to be a small minority of patients in the study), it is difficult to make a definitive recommendation in this regard.

If this technology were applied, its use would most likely be restricted to head and neck units in cancer centres in view of the specialised requirement for preparation, administration and monitoring of patients.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology in clinical practice reflects that observed under clinical trial conditions. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

There is no directly competing current therapy in this scenario. It is relatively easy to administer but does need specialist monitoring (acute reactions (about 2%), rash, cardiac toxicity). I would recommend that consideration of the use of this technology should be restricted to the 4 potential indications I listed above (with the attached caveats). The use of cetuximab should directly mirror its use in Bonner's study. As discussed above, the design of the phase III clinical trial has been rendered largely obsolete by the widespread adoption of chemoradiotherapy for stage III and IV disease. The published phase III trial sheds no light on adjuvant use of cetuximab in a post-operative setting. The adverse effects of cetuximab are acceptable (in particular it appears that there was no accentuation of acute mucositis).

Any additional sources of evidence?

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None

Implementation issues

The NHS is required by the Department of Health and Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

For patients currently receiving radiotherapy alone, treatment would change to involve weekly infusions of cetuximab. There may be a need for increased use of cardiac monitoring in patients with a history of cardiac disease. Chemotherapy administration services would be well able to cope with the technical issues of delivery of this treatment.