From: Max Partridge
Sent: 26 February 2007 22:39
To: Michelle Adhemar
Subject:
Please find enclosed my comments on the appraisal of cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck

Prof Max Partridge

Comments on the evaluation report

Overall the effects of cetuximab in the clinical setting have been disappointing with the clearest benefit shown for patients with locally advanced head and neck cancer. There is some evidence that cases with mutation of the EGFR or gene amplification show the highest benefit. The evaluation report outlines that >90% of cases with head and neck cancer over express the EGFR by a factor of 70. However this information is not included in the reference cited and may be incorrect as most studies suggest an amplification factor of about 2 when tumours are compared to the matched normal tissues.

There is no published trial data comparing cetuximab plus radiotherapy with chemoradiotherapy. The RTOG0552-phase 3 study will compare adding cetuximab to chemoradiotherapy. The evaluation does not refer to the fact that the promising results seen combining cetuximab with radiation have led to the development of new trials adding cetuximab to chemoradiation followed by maintenance with Cetuximab for advanced disease (ECOG E3303-phase 2), or delivering cetuximab and chemotherapy followed by Cetuximab and chemoradiation (NCT00226239-phase 2). The possible benefit of adding Cetuximab to post surgical adjuvant regimes with chemoradiotherapy is also being evaluated (RTOG0234-phase 2). Interim analysis from phase 2 studies using Gefitinib is available and suggests that adding EGFR inhibitors to standard treatment regimes may be beneficial and there is clearly a need for more research in this area particularly in terms of defining the benefit of biological agents with the different fractionation regimes.

In their submission Merck propose that Cetuximab might be added to radiotherapy for the 60% of cases that do not receive chemoradiation at present. The reasons why these cases do not receive chemoradiation are complex and will include clinician preference and access to facilities.

It may also be helpful to add a paragraph outlining the rationale for combining Cetuximab with radiotherapy. Exposure to radiation induces cell death but it may also induce a proliferative response and increased EGFR expression is one of the pathways that play a role in this post treatment proliferative response. Adding treatment with cetuximab may block this radiation-induced activation of EGFR thereby augmenting the effect of radiation. Blocking the EGFR may also have effects on angiogenesis and cell motility. Thus there is a sound biological basis for introducing this therapy and this is strengthened by the very significant late toxicity associated with the use of cisplatin and radiotherapy.

Comments on the Appraisal consultation document

The ACD bears the title cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck. However, the appraisal focuses on the use of cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck for whom chemoradiotherapy is contraindicated, a restricted interpretation of the licence used by the manufacturer. This discrepancy suggests that it would be helpful to define the scope of any future appraisals more precisely.

Intuitively it makes good sense to allow treatments to evolve towards more targeted and multiple tumour targeted treatments. As outlined in the evaluation the clearest benefit following treatment with Cetuximab reported to date is when this agent is combined with radiotherapy to treat locally advanced head and neck cancer. The downside of the Bonner study, on which most of the critique is based, is that it was designed at a time when radiation alone was considered as the standard treatment for patients with

advanced head and neck cancer. There is thus no comparison of cetuximab and radiation versus chemotherapy and radiation. However, the Bonner study does show that Cetuximab can augment the response to radiotherapy. This trial provided important "proof of principle " data illustrating that targeting a key signalling pathway can improve the response to radiotherapy. Indeed the benefit of cetuximab plus radiotherapy in achieving a 10% improvement in overall survival over 3 years is broadly similar to the estimated 5-14% improvement in survival with chemoradiation over 5 years, with the estimate being 12% for cisplatin. This point is understated in the evaluation report but the picture is complicated by the fact that many cases included in the Bonner study were treated by accelerated or boost radiotherapy regimes.

The ACD concludes that cetuximab should not be approved for cases for whom chemoradiotherapy is contraindicated but arguably this is not the context in which the appraisal should be conducted if head and neck cancer patients are to benefit from this agent. The report has considered the Bonner study in detail and summaries the clinical and cost effectiveness and resource implications for the NHS in the context of radiotherapy alone versus erbitux and radiotherapy and these data seem reasonable.

The Evaluation report presupposes that cetuximab would be reserved for those
cases that were not considered fit for chemoradiation. At present chemoradiation is evolving to be the standard of care in the UK but less than half of all cases that might benefit from combined treatment receive cisplatin. As highlighted by Dr Slevin, difficulty swallowing is the major problem after chemoradiation. The results following attempted salvage surgery for recurrence after chemoradiation are also poor and overall surgical morbidity is very high such that there is a need to find effective alternatives to cisplatin. Thus if Cetuximab were available, considering the relatively favourable toxicity profile, this agent might be used increasingly for those cases considered most likely to benefit from aggressive adjuvant therapy. Any recommendations should be considered in the context of the potential broader application of the

drug since radiation therapy alone is no longer the standard of care for cases with locally advanced head and neck tumours.

The ongoing clinical trials do not address the requirement to compare cetuximab and radiotherapy with chemoradiation, and the acute and chronic toxicities associated with Cisplatin will preclude use of this drug with accelerated fractionation and boost regimes that may be beneficial when cetuximab is given.

It makes sense to look for alternatives to cisplatin and consider treatment with Cetuximab for cases who are too old, have a poor performance status or unlikely to tolerate the side effects of cisplatin and radiotherapy.
Cetuximab is currently available in Scotland for these indications. It is generally accepted that we will see a transition towards more and multiple targeted therapies and there may also be merit in allowing Cetuximab to be considered as an alternative to cisplatin and radiotherapy in the management of locally advanced disease in view of the good response rate and favourable toxicity profile.

In conclusion, there is good evidence that this treatment improves outcome for head and neck cancer patients with radiotherapy to justify recommending approval for this agent in the treatment of locally advanced disease together with radiotherapy.

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