The Bone Cancer Research Trust

Mifamurtide for the treatment of osteosarcoma – Comments on the ACD

Has all the relevant evidence been taken into account?

The Appraisal Committee has considered the relevant clinical trial, but it has failed to take account of important information in that trial. The trial demonstrated a reduction in mortality of 30% which, given that the current UK survival rate is about 60%, means that around 10 young people would benefit from the treatment and live a more or less normal lifespan.

The emphasis that NICE places on relative effectiveness leads it to ignore the **absolute** benefit that 10 more young people with osteosarcoma will survive each year.

The other element which NICE has failed to take into account, and we accept that there is no published data on this, is the impact of the illness and premature death of a young person with osteosarcoma on other family members. We can say categorically that the impact is profound and remains for many years, seriously and adversely affecting the quality of life of family and friends. This impact will undoubtedly impact on the health of the family although this hasn't been formally assessed.

We note that the comment by Andrew Dillon about the outcome of the appraisal 'It is important to remember, though, that other, effective treatments are available in the NHS for treating this condition.' We would be very interested to learn what are these other treatments which deliver the same benefit as mifamurtide because we do not know of any. To the best of our knowledge, there is no alternative to mifamurtide.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

BCRT absolutely refutes the Appraisal Committee's interpretation of the clinical effectiveness data considered.

Trial INT-0133 was an investigator-led trial which NICE acknowledges was designed with the primary endpoint of overall survival but powered for disease—free survival as a two by two factorial design. That is, it was designed to be analysed as chemotherapy alone *vs* chemotherapy with mifamurtide. The ERG requested six post-hoc analyses which the study was not designed nor powered to answer. BCRT believes that this post-hoc, unplanned analysis is invalid and the numbers that result are too small to be of relevance, making these analyses unreliable and inappropriate. Notwithstanding the inappropriateness of the analysis, in the single arm comparison of regimen A vs A+ there is evidence, although it is not statistically significant, of benefit for mifamurtide.

That it is not statistically significant is entirely explained by the fact that the trial was never powered for this analysis.

The BCRT is prepared to provide a more detailed rebuttal of the ERG's conclusions about efficacy if requested.

The utility values for the use of mifamurtide are based on EQ5D which is a measure completely inappropriate to the population being considered. The tool is too blunt to reflect the ability of young people to adapt to disability and whose life is not measured in the way that adults might measure life. EQ5D falsely reduces the quality of life of people with osteosarcoma and should not be used in this setting.

Regardless of whether this is the first new treatment in 20 years for osteosarcoma, it is an effective treatment which saves lives. The ICER is a wholly inappropriate basis for a decision on whether or not mifamurtide should be made available.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

The conclusions drawn by the appraisal committee are unsound and based on a post-hoc analysis which in other settings NICE would criticise. For the reasons outlined above, the conclusion does not reflect the trial data and hence the recommendation is flawed. The NHS should not decide whether young people can be treated with mifamurtide based on a completely unreliable analysis performed by a technical group without expertise in treating osteosarcoma.

It is worth pointing out that other orphan drugs are not subject to a NICE appraisal and more expensive drugs are in routine use in the UK. It is unacceptable that young people with osteosarcoma are denied a potentially life-saving treatment because of the review mechanism to which it has been subject. NICE's appraisal should take account of these special circumstances and adjust its cost effectiveness threshold accordingly. One example, which demonstrates very well the different outcomes using different assessment methods, is the provision of the monoclonal antibody eculizumab for the treatment of patients with paroxysmal nocturnal haemoglobinuria. Introduced in April 2009 a new central funding stream, the PNH service, was added to the portfolio of the National Commissioning Group. The University of Birmingham undertook a rapid systematic review of the treatment published in 2008 and estimated that the ICERs range likely lies between £0.5M and £1.4M per life year gained for patients like those recruited to clinical trials and between £2.8M and £3.2M per life year gained for all diagnosed patients. The report also states that first year of treatment costs £252,000 and a subsequent year costs £245,700, compared to a total one-off treatment cost of £114,000 for mifamurtide.

Are there any aspects of the recommendations that need particular consideration to ensure NICE avoids unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

Since the population considered – young people with a limb amputation – is already disabled and if they survive will place further demands on the NHS because of their disabilities, the NICE approach to assessing the value of treatment discriminates against them. The young people for whom mifamurtide is effective will live a more or less normal lifespan and as such will need to use the NHS for aspects of their disability as well as illnesses experienced by the general population. While this may not be an unlawful discrimination it is certainly discrimination against the patients because of their age and the additional time they may hope to live.