Formal submission in the health technology appraisal for the use of Bevacizumab and Cetuximab for the treatment of advanced colorectal cancer

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The place of Bevacizumab and Cetuximab within current practice

Much has been written about the treatment and prognosis of advanced colorectal cancer. There are already NICE guidelines for the use of drugs including 5 Fluorouracil (5FU), Irinotecan, Oxaliplatin and Capecitabine in the treatment of advanced colorectal cancer, both for first line treatment and subsequently. Although these guidelines exist and appear to be adhered to by and large, there remain geographical variations within current practice. The Christie Hospital has a catchment population of over 3 million patients and there are satellite clinics throughout the area. There are variations in the treatment of advanced colorectal cancer within these District General Hospital clinics, depending on local pharmacy agreements between the Christie and the Hospitals. There are variations for the individual depending on whether the patient is willing to the cancer centre (Christie Hospital). There are also differences in the use of Irinotecan between the North West Network and other networks in that some patients can be offered Irinotecan first line and others cannot. There are also differences because of eligibility for trials. Thus even within the largest network in the UK there are many differences both within the network and between it and its neighbouring cancer networks.
Despite this there appears to be a quite uniform opinion between those Consultants at the Christie Hospital who treat advanced colorectal cancer. We meet regularly and there are written guidelines which we published for the network even though as indicated above variations exist. Our overall approach is to work within the NICE guidelines and drug budgets to the best of our ability and to consider patients for trial whenever suitable. Thus when it comes to the advent of new drug treatments such as Bevacizumab and Cetuximab. There exists a general consensus that outside of ongoing clinical trials we would like to see it used in accordance with the best published work.

Currently Bevacizumab and Cetuximab already used in trials or for occasional private patients. Because of variations throughout the cancer network which radiates from the Christie Hospital, the Colorectal Disease Orientated Group would like these new drugs to be used solely within the Christie Hospital, at least initially. This could eventually alter and depending on the level of support available at particular District General Hospital clinics. Within the Christie there are facilities to use these additional drugs and work within trials. The one obvious exception to this is the need to monitor patients closely when they initially are placed on the drugs because of the possibility of allergic reactions to these new antibodies. Our experience in the use of clinical trials is that patients should therefore only be treated when there is a consultant-lead clinic taking place at the same time so that doctors are available for any problems which may arise during administration of the drugs. This necessitates an increased burden on both medical and nursing time and
ideally there should be a nurse available to monitor such patients undergoing treatment
and to liaise with the medical staff if necessary.

Sub-groups of patients for whom Bevacizumab and Cetuximab are appropriate
At present, as these drugs are not approved the clinical guidelines at the Christie Hospital
only allow for these drugs to be given within the context of a clinical trial, which has
been fully funded usually by the relevant drug company. There are specifically two types
of patient group for whom these drugs are being used.

A) Bevacizumab has been used in pharmaceutical company sponsored clinical trials
as first line therapy for patients with good WHO performance status 0 or 1 as first line
therapy with no specific age limit in general for entering patients into trials. It is
imagined that the sort of patients who typically will be given Bevacizumab outside of the
clinical trial will have a WHO performance status of 0 and be aged 60 years or younger.
The only problem with this approach is that it is not possible to be completely dogmatic
as occasionally very fit patients above the age of 60 will be eligible, or for example there
may be a very fit man for his age in his 30s, but who for one reason or another has a
WHO performance status of 1. Nevertheless, only very fit patients undergoing first line
treatment would ever be considered for this drug outside of clinical trials until further
evidence exists. For the others who might wish to have this drug we would consider
entering into the COIN study currently being run by the NCRI.

B) Cetuximab has been used within a recently completed second line study for
patients of WHO performance of 0 or 1 who have advanced colorectal cancer and have
progressed following with Irinotecan containing regimes as first line treatments (Bond study). There are relatively small numbers of such patients, but again outside of a clinical study I could envisage the patient who will be eligible for such treatment would have a performance status of 0 or 1 and probably have had an initial good response to Irinotecan before progressing. At this stage, such patients should be considered as candidates for the addition of Cetuximab to Irinotecan.

There has also been a small number of patients given third line chemotherapy at the Christie with advanced colorectal cancer. An audit of 28 of these patients given a variety of treatments showed a poor partial response rate of 10%. We would therefore only occasionally consider offering Cetuximab and Irinotecan as third line therapy for patients with WHO performance status 0 to 1 who have previously been given Irinotecan and have shown an initial response to this before progressing.

Advantages and Disadvantages of these drugs
The increasing use of antibodies in the treatment of advanced colorectal cancer does add an additional layer of complexity into the treatment of the disease. As stated above there is a small risk of a serious allergic reaction in using these drugs (published data suggests less than 5%), though this risk is small. Nevertheless in view of this patients need to be carefully monitored during the infusion. This does take up extra clinical space and occasionally will require quite major medical intervention if e.g., a patient were to have an anaphylactic reaction. Most of all there is a requirement for additional nursing supervision during treatment.
The number of patients who will be eligible for such treatments remains small, even at a centre as large as the Christie Hospital. There is an estimate from the recruitment rate at our own in-house study using Bevacizumab in the first line treatment of advanced colorectal cancer that there are no more than 50 patients a year who might be eligible for the drug outside of a clinical trial. At present these patients would be entered into the COIN study where possible. Other patients would decline the treatment for a variety of reasons and it is likely that 25-30 patients per year would be treated once the COIN study has finished at least initially. An approximately similar number would be considered for second line treatment with Cetuximab with very few indeed considered for third line treatment, probably no more than 5 per year. I would also estimate that the number is also likely to rise as technology becomes more likely available, particularly if the published work on the use of Bevacizumab in first line treatments (Hurwitz et al and Kabbinavar et al) are confirmed by the NCRI COIN study. Having used these drugs within trials and also on occasion for private patients, my personal experience is that in common with other newly introduced drugs the handling of the drugs and the side effects becomes easier with time.

The limited use of these drugs within trials at present broadly supports the outcomes observed and published of clinical studies already in existence. (eg Hurwitz et al, Kabbinavar et al, COIN study) The most important outcomes of overall survival and in quality of life appear to have been adequately measured within these studies and will be measured adequately in the ongoing trials. The only adverse side effects which have
come to our attention and are not particularly emphasised in the published work to-date is that Bevacizumab potentiates diarrhoea when used with Irinotecan and 5FU or Capecitabine which has sometimes required a dose reduction of about 20% in these drugs.

Additional sources of evidence
I am not aware of any additional sources of evidence apart from those already entered into the guideline briefings given apart from any in-house work data owned by either ROCHE or MERCK for Cetuximab which they should already have sent to you.

Implementation issues
There will be no specific problems with implementation of these drugs over and above the increased medical and nursing resources stated above, in particular, a designated nurse who would need to monitor patients closely while receiving their infusions looking for allergic reactions. There would also be additional use of treatment rooms whilst these infusions were taking place, although the numbers of patients treated will be a minimal increase.

Non-implementation issues
Although much is written quite correctly about the implementation of these drugs there are also issues which must be considered if the drugs are not in anyway implemented in the National Health Service. The main impact is that when a drug is available in the NHS even within well defined constraints, patients who will benefit will find their way through
a major cancer centre such as the Christie to the drug. Patients who are not suitable to be
given the drug usually because of poor medical fitness can normally have the decision
explained to them and are generally accepting. If, however, there are patients often very
fit and, increasingly well read on the available literature who realise the drug would be
suitable for them, but realise that they are not offered it because of financial constraints,
then much time is taken up, by the Consultant, his junior staff, the nursing staff, the
secretaries and the hospital management in explaining the reasons behind this in what is
often an emotionally charged atmosphere. I believe there is insufficient work available
on the amount of time and the cost to the NHS taken up. If explained to fit patients that a
drug cannot be made available for them for financial reasons a small number of these
patients will opt to pay for the drug privately, but most will not be able to do so. A
typical example would be a 40 year old man with a young family who would have to
mortgage his house to pay for the drugs for himself, but who being articulate is able to
understand that the drug is not being made available to him because of economic reasons.
It is normally necessary for the consultant and his team to spend a minimum of 2 or 3
hours explaining to such patients the reasoning behind this. At the minimum this has a
knock on effect on the number of patients with complex issues who need to be discussed
and seen by the consultant, which inevitably in my experience causes a rise in the waiting
list for new patients to be seen for complex issues to be resolved and also complaints. On
the other hand, if funding is available even for a small number of patients those who are
eligible will usually receive the drug and others who do not quite meet the criteria are
usually more understanding of why they are simply not fit enough for such treatment
without the cause for long consultations.
Summary

The Christie remains the largest single Oncology Centre in Europe and is gaining experience in the potential benefits of Bevacizumab and Cetuximab in advanced colorectal cancer. In view of the size of the North West Cancer Network there are variations in the use of drugs for advanced disease. Nevertheless, we have been successful in selecting patients for inclusion in trials using these two drugs through out cancer network and close work with colleagues within our own stringent guidelines. Our limited use of the drugs to-date suggest that there are small numbers of very fit patients who would benefit from the use of these antibodies in first line and second line treatment and very occasionally third line also. It would seem reasonable to support use of these exactly as laid out in the submission document, ie Bevacizumab as first line treatment and Cetuximab as second or occasionally third line use in combination with Irinotecan in patients previously given Irinotecan. There are modest implications to the delivery of care if these drugs were used, especially as the number of patients treated would be small. There are increasingly major issues surrounding non-implementation of these drugs. The Christie Hospital therefore looks forward to working with our partners at NICE to see these drugs implemented alongside the ongoing NCRI COIN trial.

References
