National Institute for Health and Clinical Excellence

The use of Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.

Royal College of Nursing

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Introduction

With a membership of over 370,000 registered nurses, midwives, health visitors, nursing students, health care assistants and nurse cadets, the Royal College of Nursing (RCN) is the voice of nursing across the UK and the largest professional union of nursing staff in the world. The RCN promotes patient and nursing interests on a wide range of issues by working closely with Government, the UK parliaments and other national and European political institutions, trade unions, professional bodies and voluntary organisations.

Evidence Submission

The RCN welcomes the opportunity to submit evidence to inform the appraisal of the use of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer

Population

Patients with metastatic colorectal cancer.

Bevacizumab (Avastin) is used in combination with intravenous 5-fluorouracil/folinic acid (5FU/FA) or intravenous 5FU/FA plus irinotecan and is indicated for first-line treatment.

Cetuximab (Erbitux) is used in combination with irinotecan and is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy.

Current Practice (current standard treatment)

In the main, the evidence submission has been obtained from reviewing cancer services offered at the Greater Manchester and Cheshire Cancer Network, which is the largest in the United Kingdom. Current standard treatment for the above group of patients in this network is based on

irinotecan/5FU/FA and/or oxaliplatin/5FU/FA. An oral fluoropyrimidine may be substituted for 5FU/FA in certain cases, such as patient choice, or clinical decision. These drugs are Capecitabine or Tegafur and uracil (the latter in combination with folinic acid). In certain cases (such as cardiac disease) patients may be offered treatment with Tomudex. Mitomycin C may sometimes be used and those patients whose performance status is too poor to tolerate active treatment with cytotoxic therapy may be managed with best supportive care.

Patients who have potentially operable liver metastases will receive treatment with oxaliplatin/5FU/FA (or oral fluoropyrimidine) in an attempt to down-stage their disease to render them operable (with curative intent).

No specific treatment regimens have been described as it is acknowledged that there will be geographical variation in drug administration throughout the United Kingdom.

Advantages and disadvantages of standard treatment

The advantage of irinotecan and 5FU/FA is that once irinotecan comes 'off patent', treatment will be relatively cost-effective. Infusions are quick to administer and the 5FU/FA is given via a pump. Side effects and toxicities are usually minimal and well tolerated. Recognition and early dose reduction or deferral, forms a large part of prevention, particularly with neuropathy from oxaliplatin. Tomudex should be prescribed with caution under strict supervision and renal function monitored carefully. Mitomycin can be seen as an 'easy option' but patients can quickly become immunocompromised and education and regular monitoring of full blood count is vital. However, it is a quick, bolus injection which is given once every six weeks and from that point of view it is usually acceptable to the patient.

Disadvantages of most of these drugs is that patients face the inconvenience of attending the oncology centre on at least a fortnightly basis, and sometimes more frequently. This can add a financial burden in terms of travelling expenses and sometimes loss of earnings, if not for the patient, then for their carer. Car parking also incurs a fee. Patients have to wait for long periods of time in busy out-patient clinics and there is often a delay in the preparation of the drug in pharmacy. Patients will usually spend most of the day at the hospital.

Another disadvantage is that if patients are going to receive infusional 5FU/FA they will need to have either a Hickman line or PICC (peripherally inserted central catheter) inserted and these can have a negative impact on quality of life and body image. They also pose additional risks of thrombi.

Advantages and disadvantages of new technologies

In terms of benefit, probably the main advantage is the increased median survival time with the new therapies. This was 20.3 months for bevacizumab plus 5FU/leurovorin compared with 15.6 months for 5FU/leucovorin plus

placebo (Hurwitz et al 2004). The median survival time for cetuximab plus irinotecan was 8.6 months and 6.9 months for cetuximab alone (Cunningham et al 2004). Treatment regimens, certainly for bevacuzimab, can be flexible which should impact positively on quality of life. Before the introduction of cetuximab for irinotecan refractory disease, there was little to offer patients once their disease progressed. However, they can now be re-challenged with irinotecan plus cetuximab and the Appraisal Committee will be aware of the results of the BOND study (Cunningham et al 2004).

The main disadvantages are that these drugs are still very much in their infancy and we need to carry out more randomised trials to fully appreciate their potential. Bevacuzimab, in particular, has still not been used as second-line treatment, when patients may already have been heavily pre-treated.

Whilst the expected toxicity profile is manageable (skin rash with cetuximab, and hypertension, reduced wound healing, and diarrhoea with bevacuzimab) patients are still at risk and should be monitored carefully. Patients who do experience the skin rash from cetuximab can experience negative body image but when they realise that the severity of rash usually correlates to the degree of response they are happy to continue treatment. The rash usually responds to the administration of tetracycline-based antibiotics.

Other comments

Treatment should only be administered within the confines of a specialist oncology centre by experienced personnel who are skilled in the management of these therapies, as anaphylaxis can occur, particularly with cetuximab. Appropriate adjuncts such as adrenaline, hydrocortisone and piriton should be readily available for immediate administration. Patients receiving bevacuzimab should initially have their blood pressure monitored regularly as this drug can cause changes in the permeability of vessel walls, leading to hypertension. Wound healing can also be compromised due to the anti-angiogenic effects.

All patients receiving these therapies should be offered additional support from community nurses to specialist colorectal nurses and Macmillan nurses.

Finally, this group of patients have advanced disease, which in the majority of cases cannot be down-staged. The NHS Cancer Plan (2000) pledged a commitment to improving treatment and reducing cancer mortality by providing patients with the best care and professional support by tackling inequalities in health and treatment. It would seem unethical to deny patients treatments that are more effective and which possibly could result in a longer survival time.

References

Cunningham, D. et al (2004) Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. The New England Journal of Medicine. 351:337-345.

Hurwitz, H. et al (2004) Bevacizumab plus irinotecan, fluorouracil, and Leucovorin for metastatic colorectal cancer. The New England Journal of Medicine. 350:2335-42.