The use of Oxaliplatin (in combination with 5FU / FA) and Capecitabine for adjuvant treatment of colon cancer

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Thank you for the opportunity to submit a personal statement to inform the appraisal of the use of Oxaliplatin and Capecitabine for adjuvant treatment of colorectal cancer.

Population

Dukes C colon cancer following surgical resection of the primary tumour.

CURRENT PRACTICE
Current standard treatment

Within the Greater Manchester and Cheshire Cancer Network (the largest in the UK), the current standard adjuvant treatment is weekly IV bolus 5FU / FA for 30 weeks.

The QUASAR collaborative group study reported no difference between Mayo scheduling (standard regimen in the USA) or weekly x 30 weeks in terms of disease-free survival (DFS) and overall survival (OS). However the weekly regimen resulted in significantly less stomatitis, diarrhoea and neutropenia and now has been widely adopted.

It is recognised, however that there remains significant geographical variation in the 5FU-based regimens currently in use in the UK.

For specific high-risk Dukes B patients (presenting with obstruction, perforation, locally invasive tumours, T4 tumours, evidence of vascular invasion and poorly differentiated tumours) 5FU/FA IV bolus chemotherapy is also considered as these patients have a prognostic outlook similar to Dukes C stage patients.

For specific high-risk Dukes C patients (as above, and including multiple involved regional lymph nodes) there is already some Capecitabine and Oxaliplatin / 5FU / FA usage within this network, as this group of patients will also have a poorer prognostic outlook.

Advantages and disadvantages of standard treatment

The advantage of the current bolus IV 5FU / FA is that is quick and cost-effective.

The disadvantages include the inconvenience for patients of attending hospital weekly, the financial burden that this may impose on them, travel and parking difficulties etc, a less favourable toxicity profile and the significant input of staff resources in out-patient and chemotherapy clinics, in addition to pharmacy preparation of the drug. Additionally a small proportion of patients are needle-phobic and this necessitates the placement of a central venous catheter or peripherally inserted central line.

IV therapy may also have a negative impact on quality of life.

NEW TECHNOLOGIES
Advantages and disadvantages of adjuvant Capecitabine

The appraisal committee will be aware of the results of the X-ACT study which reported a superior safety profile and improved recurrence-free survival in Dukes C patients treated with Capecitabine compared to bolus 5FU / FA (Twelves et al 2005). Disease-free survival and overall survival were equivalent in both arms. Capecitabine was particularly well tolerated and hospitalisations due to adverse events were significantly less common in patients treated with Capecitabine.

The scheduling of Capecitabine at three weekly intervals is much more convenient for patients. It also releases outpatient clinic space, reduces throughput in chemotherapy treatment areas and reduces the burden on pharmacy services.

Recently presented findings from the X-ACT study at the American Society of Clinical Oncology (McKendrick et al 2004) showed that 6 months of adjuvant treatment with Capecitabine provided a substantial reduction in medical resource use (in excess of 100 hours per patient) compared to the standard bolus 5FU / FA. Such resource savings are an important consideration in the NHS, given existing staff shortages and prolonged waiting times for treatment.

The disadvantage of adjuvant Capecitabine is that it costs more than IV 5FU/FA when drug acquisition costs alone are considered. This is offset, to a large extent, by the reduced medical resource use already alluded to.

Quality of Life (QOL) and Patient preference in relation to Capecitabine

When given a choice, most cancer patients prefer oral therapy instead of IV therapy, but only if treatment is equally effective (Liu et al 1997, Borner et al 2001). Patients cite increased convenience, less distress over repeated IV access and more control over their own treatment as major factors. These findings indicate that the efficacy, safety and convenience benefits of Capecitabine enable patients to maintain a more normal lifestyle during treatment and impact positively on QOL.

The introduction of Capecitabine in the adjuvant setting would necessitate an appropriate standard of home-based oncology care, as a large part of patient management would be shifted to patients themselves and their carers. A crucial element of using Capecitabine is educating patients to recognise toxicity that necessitates prompt interruption of treatment. Clinical evidence indicates that patients, with appropriate instruction, are willing and capable of managing their treatment and any associated toxic effects in the home setting. Given the widespread use of capecitabine in the CRC metastatic setting, many primary health care services are already familiar with oral chemotherapy.

All patients treated with capecitabine have access to ‘Roche home-care’ nursing services. Discussions between RCN and Roche are ongoing with the objective of establishing an accredited oral chemotherapy course for nurses in the near future.

Advantages and disadvantages of adjuvant Oxaliplatin / 5FU / FA

The appraisal committee will be aware of the results of the MOSAIC study which suggests a role for using Oxaliplatin 5FU / FA in the adjuvant setting. DFS was superior in the Oxaliplatin treated cohort. This regimen involves fewer hospital visits

over a six-month period: 12 OP appointments as opposed to 30 for weekly bolus treatment.

However peripheral neurotoxicity was a significant side effect in this study and 18 months following completion of treatment 3.9 % of patients had persistent debilitating Grade 2 / 3 symptoms.

While *routine* use of combination Oxaliplatin / 5FU / FA in the adjuvant setting might not be safe or practical, there is nonetheless a subgroup of high-risk Dukes C patients who would probably benefit from having more aggressive combination treatment as opposed to the current standard. Clearly the risks and benefits of a more toxic regimen and the requirement to place a central venous catheter would have to be assessed in each individual patient.

Adjuvant Oxaliplatin and infusional 5FU costs are higher than weekly bolus 5FU but again this expenditure may be offset by improved survival of Dukes C patients, thereby reducing the financial burden of subsequent metastatic treatment.

OTHER COMMENTS

The evidence of efficacy for Capecitabine and Oxaliplatin has resulted in regulatory approval for these drugs in this indication by both the FDA and EMEA. As a result, these drugs are regarded as an effective and superior alternative to bolus 5FU/FA in the adjuvant treatment of colon cancer and both are already in widespread use in the private sector.

The NHS Cancer Plan (2000) stated a commitment to improving treatment and reducing cancer mortality by providing patients with the best care and professional support and tackling inequalities in health and treatment. It would seem unethical to deny patients treatments that are more effective, more convenient and result in improved QOL in the adjuvant setting.

A plethora of health related information available to the public and NHS users results in many individuals specifically requesting therapies with proven benefits. It is professionally compromising and often difficult for health care workers to deny patients particular treatments based solely on a lack of funding. The psychological morbidity of not being able to access the most up-to-date treatments is clearly distressing for patients and carers.

All professional groups are guided by robust scientific evidence in making patient orientated treatment decisions but equally value and utilise their clinical experience and discretion in individualising care in complex situations such as adjuvant colon cancer patients with a poorer prognostic outlook. The approval of these new technologies would allow flexibility in determining the most appropriate treatment for each patient.

Within the oncology nursing community throughout the NHS, there are qualified and experienced specialist cancer nurses providing expert skills in the administration and management of chemotherapy. The introduction of Capecitabine and Oxaliplatin / 5FU / FA in the adjuvant setting would fit into the existing comprehensive service.

Finally, the difficulties encountered with ‘postcode prescribing’ in relation to metastatic colorectal cancer chemotherapy must be avoided in the adjuvant setting. Strategic Health Authorities have already provided funding for adjuvant Capecitabine

in some areas. Failure to approve these new technologies for the adjuvant treatment of colon cancer will perpetuate an already developing inequitable service for patients.

References

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