PERSONAL STATEMENT BY PROFESSOR C G MARKS

Health Technology Appraisal

Oxaliplatin and capecitabine for the adjuvant treatment of colorectal cancer

I am a Consultant Surgeon at the Royal Surrey County Hospital and Visiting Professor of Surgical Oncology at the University of Surrey, Medical Director of South West Surrey and Hampshire Cancer Network, Past President Association of Coloproctology of Great Britain and Ireland, Section of Coloproctology of the Royal Society of Medicine and the St Mark's Association. I have been a member of the Colorectal Committee of the UKCCCR and at present am a member of the Adjuvant Chemotherapy Group for Colorectal Cancer of the NCRN and the Rectal Cancer Sub Group. I have contributed to many trials of adjuvant chemotherapy as a major contributor to AXIS, QUASAR as well as MRC trials of radiotherapy.

In my practice I have dealt with a very large number (more than 1500) of patients suffering from colon and rectal cancer over the last 25 years. During the last decade there has been a revolution in the adjuvant chemotherapy treatment for colonic cancer, and to a lesser extent for rectal cancer for which the evidence for adjuvant chemotherapy is much less compelling.

The timing and duration of adjuvant chemotherapy need to be examined critically. For colonic cancer 5FU +/- folinic acid has been the mainstay of treatment with a response rate of 27%, defined as reduction in tumour size or stable disease, in advanced cancer. Originally these drugs were often given in the adjuvant context for up to one year, however latterly adjuvant chemotherapy has been given for six months, for example the X-ACT trial for 28 weeks, or indeed shorter periods for one week only postoperatively in the AXIS trial.

The route of adjuvant chemotherapy. For solid tumours, particularly colonic cancer, most adjuvant chemotherapy has been given intravenously with the patient needing to attend for treatment at hospital, usually an oncology unit with an up to 48 hour stay.

Capecitabine, which has been shown to be equivalent to 5FU/folinic acid (X-ACT trial) can be given **orally** and clearly this represents a potential benefit to the patient although it must be borne in mind that Capecitabine has toxic side effects. Patients and their carers must be informed about this. There may also be an opportunity for cost savings if Capecitabine replaces 5FU/folinic acid because it can be given as an outpatient or even at home.

Oxaliplatin. I have previously referred to the response rate to 5FU/folinic acid as being of the order of 27%. When Oxaliplatin is combined with 5FU/folinic acid the response rate for advanced tumours approaches 52%

Oxaliplatin however is given intravenously. There are numerous side effects, particularly neurotoxicity, which results in dose modifications or indeed patients having to stop this regime of chemotherapy. Finally, the cost of Oxaliplatin is considerable.

Which patients should be offered chemotherapy

There is little doubt that Oxaliplatin should be offered to patients with Dukes' C (Stage III, N1/N2) disease. These are patients with tumour deposits in the lymph nodes and are therefore a fairly easy group to identify.

In contrast, certain Dukes' B T3/4 N0 (Stage II) tumours may benefit from chemotherapy. The Mosaic Study has defined "bad" Dukes' B tumours as follows:

- T4 (perforates the surroundings of the bowel or directly invades other organs or structures)
- Bowel obstruction
- Tumour perforation
- Poorly differentiated tumour
- Venous invasion
- Number of examined lymph nodes less than 10

In the Mosaic study of adjuvant treatment the benefit in terms of disease-free survival of giving 5FU/folinic acid combined with Oxaliplatin for Stage III tumours compared with 5FU/folinic acid was 8.6%, for all Stage II tumours

was 3.5% and for the selected sub group of “bad” 5.4%. At present when all patients given the two treatments are compared in terms of overall survival at five years the difference is 2.1% in favour of the group receiving Oxaliplatin. When the patients are divided according to the staging of their tumours, however, there is no difference in overall survival for the Stage II group whereas there is a benefit of 3.2% in favour of the Oxaliplatin group in patients with Stage III tumours after 56 months of follow up.

The NSABP C-07 trial was a similar study comparing 5FU/folinic acid with and without Oxaliplatin. At three years the Oxaliplatin group had a 76.5% (compare Mosaic 77.9%) disease-free survival compared with 71.6% for the standard regime. These data confirm the results of the Mosaic trial.

The future

There are many studies to identify those tumours which will respond to adjuvant chemotherapy. Standard histological and histochemical methods are used and it is hoped that in due course molecular markers of tumour type and activity will allow focused chemotherapy in contrast to the present rather blunderbuss approach.

Although the best results following adjuvant chemotherapy show single-figure increases in disease-free survival and overall survival, it must be remembered that there are approximately 35,000 new cases of colorectal cancer in the United Kingdom each year and at any time approximately 80,000 patients alive with diagnosed cancer of the large bowel.

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