Oxaliplatin and capecitabine for the adjuvant treatment of colorectal cancer

A submission of evidence to the NICE Health Technology Appraisal Committee on behalf of the Royal College of Physicians, the Royal College of Radiologists, the Association of Cancer Physicians and the Joint Collegiate Council for Oncology

Introduction

There are approximately 22,000 new cases of colon cancer diagnosed annually in England and Wales. Colorectal cancer is thus the third most common cancer in the UK after breast and lung cancer. The incidence of colon cancer rises steeply with age and over half of all deaths are in patients over 75 years. In the UK the Dukes classification remains the most commonly used staging system for colon cancer and at diagnosis only 10% of patients have a Dukes A tumour (confined to the bowel mucosa or submucosa) the remainder being equally distributed between, Dukes B (into or through muscle wall but with no regional node involvement), Dukes C (involving regional lymph nodes) and Dukes D (distant metastatic disease). Approximatelty 85-95% of patients with Duke A disease and 60–80 % of patients with Dukes B cancers will be cured by surgery alone but for Dukes C patients this falls to 30–60% depending on extent of nodal involvement with an average of around 50%. For patients who present with metastatic colon cancer the five year survival is less than 10% thus overall some half of all colon cancer patients will eventually die from their disease.

Adjuvant systemic therapy following apparently curative resection of a primary cancer is designed to eradicate micrometastases and thus reduce the risk of recurrence. Adjuvant chemotherapy for colon cancer based on 5-Fluorouracil has been studied for over 40 years but it was not until the late 1980s that convincing evidence of a survival benefit was established. More recently research has centred around the contribution of modulating agents such as levamisole and folinic acid and the mode of delivery and duration of 5 FU chemotherapy. The results of many large scale trials have shown that levamisole makes no contribution and that low dose folinic acid is as effective as higher doses in enhancing the effect of 5FU. In addition continuing beyond six months therapy does not provide any additional survival advantage and, in contrast to the situation in advanced colorectal cancer, bolus regimens appear to be as active as infusional treatment. At the present time therefore the recommendations for the adjuvant treatment of Dukes C colon cancer are that all patients who are fit enough should receive six months intravenous chemotherapy with a 5FU + folinic acid regimen. Pooled data suggest that this will increase the disease free survival at 5 years from 42 to 58% and the overall survival from 51 to 64%.[(1)]

Capecitabine

5FU administered orally undergoes significant metabolism in the wall of the GI tract and the liver resulting in extensive intra and inter-patient variation in bioavailability. Capecitabine is a rationally designed precursor of 5FU which can be taken orally and which is metabolised by a series of enzymatic steps to the parent drug. The final step involves the enzyme thymidine phosphorylase which occurs in greater concentrations in tumour tissue in comparison with normal tissues and thus capecitabine therapy may benefit from an element of targeting. Capecitabine was initially shown to be as effective as bolus 5FU for the management of advanced colorectal cancer and subsequently a large scale randomised trial has compared these treatments in the adjuvant setting. The X-ACT study randomised 1987 patients with resected Dukes C colon cancer to six months of single agent capecitabine or six months 5FU + folinic acid using the daily x 5 Mayo Clinic schedule.[(2)] The trial was powered to demonstrate equivalence with disease free survival as the primary end point. The preliminary results of this trial were reported at ASCO in 2004. With a median follow up of 3.8 years capecitabine was at least equivalent to 5FU with some suggestion of superiority in terms of three year DFS (64.2% vs 60.6% p=0.052) and overall survival (81.3% vs 77.7% p= 0.07). Capecitabine therefore appears to be a viable alternative to intravenous bolus 5FU + folinic acid as adjuvant therapy for Dukes C colon cancer.. Moreover the use of capecitabine has significant advantages in terms of pharmacy, out-patient chemotherapy unit and chemotherapy nurse resources all of which are under continuous and mounting pressure. Thus 8 cycles of capecitabine would not require the use of pharmacy aseptic isolator time and would only need 8 visits to the chemotherapy unit. Six months of 5FU + foloinic acid requires 30 iv doses to be prepared and 30 outpatient visits for treatment administration. A unit serving a population of 2 million might be expected to deliver around 400 iv bolus doses of 5FU + folinic acid per month as adjuvant colorectal cancer chemotherapy. Conversion to capectabine would mean that a significant amount of pharmacy isolator time could be deployed elsewhere and there would be additional savings of over 200 outpatient visits and chemotherapy specialist nurse episodes. On the other hand the toxicity of 5FU + folinic acid given by the weekly schedule is minimal with very few patients requiring hospital admission to manage side effects. In the X-ACT trial capecitabine was compared with the more toxic daily x 5 Mayo Clinic schedule of 5FU + folinic acid and found to have a lower incidence of adverse effects with the exception of hand foot syndrome.[(3)] However experience with capecitabine in advanced disease has suggested that a significant minority of patients develop problems such as diarrhoea and neutropenic sepsis. Thus it is likely that hospital admission rates for the management of toxicity would rise with the widespread use of adjuvant capecitabine where it is replacing the weekly 5FU schedule. Despite this possible drawback there are clear benefits for many patients in the use of an oral therapy in addition to the potential resource savings outlined above and thus we would recommend that capecitabine should be available as an option for the adjuvant treatment of Dukes C colon cancer.

Oxaliplatin

Oxaliplatin is a platinum analogue which acts by cross linking DNA and thus preventing DNA replication and hence cell division. Oxaliplatin in combination with 5FU + folinic acid has demonstrated significant activity in advanced colorectal cancer improving response rates from around 25-30% for infusional 5FU + folinic acid to over 50% with the combination. As a result of these data a large adjuvant trial was undertaken, the MOSAIC trial, which randomised 2246 patients with Dukes C (60%) and Dukes B (40%) colon cancer to 5FU + folinic acid +/- oxaliplatin.[4] In this trial the 5FU + folinic acid was delivered using the 48 hour infusional deGramont schedule with oxaliplatin given as a 2 hour infusion on day one (FOLFOX). Treatment was repeated at 14 day intervals for 12 cycles. At a median follow up of 38 months three year disease free survival was significantly higher with FOLFOX (72 versus 65% HR 0.80) for the patients with Dukes C disease but to date there is no significant difference in overall survival. The authors argue that disease free survival at three years is an accurate surrogate for overall survival at five years citing in support the recent analysis by Sargeant et al[5], although the use of disease free survival as a primary end point remains a matter of debate. The major drawbacks to treatment with FOLFOX are that it is somewhat complex to administer and there is a significant rate of neurotoxicity. A central venous line is required to enable patients to have their chemotherapy on an outpatient basis and each visit takes a minimum of 2.5 hours of day case time. Oxaliplatin causes a unique cold related peripheral neuropathy affecting over 90% of patients during treatment with symptoms still present to a greater or lesser degree18 months after completing treatment in 24% of patients. Given the preliminary nature of the MOSAIC trial results and the concern surrounding neurotoxicity we would not recommend oxaliplatin based chemotherapy as adjuvant treatment for all patients with Dukes C colorectal cancer however it should be an option for high risk patients eg more than 3 positive nodes, or T4 lesions. It is also worth noting that the median age of the patients included in the trial was 60 yrs with an upper age limit of 75.

Conclusions

All patients who have had a Dukes C colon cancer resected and who are fit enough should be offered a six month course of fluoropyrimidine based adjuvant chemotherapy. At present the most widely used fluoropyrimidine is bolus iv 5FU modulated by folinic acid. However the results of the X-ACT trial demonstrate that capecitabine is a viable alternative and its introduction could lead to considerable savings in pharmacy, day case and chemotherapy nurse time. We would recommend that we should be able to offer adjuvant capecitabine to suitable patients but that toxicity should continue to be monitored carefully. The MOSAIC trial has shown a significant advantage for FOLFOX over infusional 5FU + folinic acid in terms of disease free survival but not as yet overall survival. In addition there are problems with neurotoxicity and thus we would suggest that FOLFOX should be available as an option for high risk Dukes C patients.

References

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