The use of irinotecan, oxaliplatin and raltitrexed in the treatment of advanced colorectal cancer (review of guidance No. 33)

Submission of the British Association of Surgical Oncology- The Association for Cancer Surgery

September 2004
Executive Summary

The original 2002 Guidance 33 from NICE recommended that UK patients with advanced colorectal cancer (CRC) receive an outdated and ineffectual treatment (5-FU + folinic acid [leucovorin]) as first line therapy, and were only eligible for effective therapy if their disease (inevitably) progressed despite this treatment.

The recommendation that, ‘oxaliplatin could be used in first line treatment if in the opinion of an experienced liver surgeon, a patient might become potentially resectable’ was unintelligible in 2002, and has turned out (predictably) to be unworkable in practice.

Since 2002, the definition of hepatic resectability with curative intent for these patients has changed radically to encompass any patient in whom a 70% liver resection will achieve total macroscopic removal of all liver disease.

Compelling evidence (detailed in the body of this submission) has emerged since 2002 that demonstrates:

• The superiority of oxaliplatin and irinotecan based regimens over 5-FU in first line therapy for advanced CRC
• The probable superiority of oxaliplatin based regimens over irinotecan alone in first line therapy
• The confirmation of oxaliplatin based regimens in sufficiently downstaging inoperable liver disease to potentially curative resectability, although it remains impossible to accurately predict the patients who will achieve maximal benefit from this approach
• The possible superiority of combination triple therapy using oxaliplatin in combination with irinotecan and 5-FU with folinic acid over other regimens in converting non-resectable disease to surgical (and therefore potentially curative) resectability

The British Association for Surgical Oncology therefore strongly recommends that NICE now issue guidance that states:

• The recommendation that ‘oxaliplatin only be given if a liver surgeon thinks that a patient might become resectable’ be discarded since it is unworkable in practice
• Oxaliplatin and or irinotecan based regimens (alone and in combination) be given as first line therapy to British patients with advanced CRC
• Consideration should be given to triple therapy (oxaliplatin + irinotecan + 5-FU/folinic acid), possibly with the newer biological agents (such as cetuximib) in second line treatment
• That this guidance can only be effective if NICE recommends that the National Cancer Plan places real investment in the expansion of liver cancer surgery services (which are presently totally under-resourced) across the country
Background

1.1

The original 2002 Guidance 33 by NICE recommended that patients suffering from advanced colorectal cancer (CRC) whose disease was not amenable to potentially curative surgery should receive combination systemic chemotherapy using a combination of 5-fluorouracil (5-FU) and folinic acid (FA). If patients failed this regimen and showed signs of disease progression then they might receive irinotecan as second line therapy. For an indeterminate group of patients with advanced (and unresectable) CRC, NICE ruled that if in the opinion of an experienced liver surgeon the disease might become resectable after chemotherapy, then these patients could receive oxaliplatin based chemotherapy regimens as first line therapy.

1.2

It has been clear for some considerable time that the availability of effective treatment for patients in the UK with advanced CRC has been prioritised primarily on financial and not clinical appropriateness (1). As a consequence of NICE Guidance 33, British patients with advanced CRC have been condemned for the last 3 years to inappropriate and historically ineffectual treatments, more attuned to the late 1980’s than the first decade of the 21st century. Since 2002, in order to possibly become eligible for effective treatment, British patients must first receive a knowingly ineffectual treatment (5-FU+FA) which at best results in a few weeks prolonged survival over best supportive care (2). Only if these people then clearly fail this ineffective treatment, will British patients then possibly be offered effective second line chemotherapy in the form of irinotecan. The currently ongoing UK FOCUS study has yet to report (due for presentation in Vienna at the European Society of Medical Oncology in November 2004). Preliminary data suggest that the median survival of patients with advanced CRC, who received sequential treatment, starting with 5FU+folinic acid and progressing to more effective second line therapy when they progressed, is of the order of 16 months. In this study, nearly 60% of those patients who stayed on protocol received second line chemotherapy, but none converted to resectability with curative intent thereafter. Furthermore, in real life, off trial, less than 30% of British patients with advanced CRC actually receive second line chemotherapy after failing 5-FU+FA.

1.3

This observation is in stark contrast to the USA and the rest of Western Europe, where patients with advanced CRC have been receiving appropriate, effective chemotherapy regimens based on oxaliplatin with 5-FU + folinic acid (FOLFOX) and irinotecan since the late 1990s. Furthermore, up to 70% of patients in North America and Europe will receive second line chemotherapy after progression on effective first line chemotherapy. Unlike 5FU+FA, where the best median survivals for patients are an increase from 6 months with best supportive care to 7-9 months (2), combination chemotherapy using oxaliplatin and/or irinotecan was shown over 4 years ago to significantly improve disease progression free survival and significantly better disease response rate over 5FU+FA alone (3-6). As a direct consequence of NICE’s Guidance
33, British patients suffering from advanced CRC have lost literally **thousands** of QUALYs between 2002 and 2004.

1.4

Internal audits of surgical activity in British hepatobiliary units has shown a real increase in activity over the last two years (2002-4), and in some units this increase has exceeded 75%. This increase in surgical activity has been seen exclusively in resection rates for colorectal liver metastases, while resection rates for primary liver cancers (hepatocellular carcinoma, cholangiocarcinoma and gallbladder cancer) have remained unchanged. As a direct consequence of this increase in liver surgical activity (**predicted by the surgeons in 2002**), waiting times for liver cancer patients for potentially life saving surgery have risen to up to 6 weeks to see a liver a surgeon and a further 10-12 weeks from seeing the surgeon to eventually coming to surgery. However, health service managers are being instructed to tell the liver surgeons to concentrate their limited resources on primary liver cancer (hepatocellular carcinoma, cholangiocarcinoma and gallbladder cancer) patients (who meet the 4 week rule with regard to treatment), over those with metastatic liver cancer (who in the eyes of the managers have already been counted once for their primary colorectal cancer, and are therefore ineligible under the 4 week rule).

1.5

Therefore, NICE guidance 33 advising that oxaliplatin based chemotherapy, ‘could be considered in first line therapy for unresectable liver only disease, if an experienced liver surgeon thought that as a result the patient might become resectable’, is at best illogical and in practice, unworkable.

1.6

Presently there are less than 40 recognised experienced liver surgeons working in the NHS across the UK. It is a physical impossibility for this very limited number of surgeons to input into every DGH colorectal MDT across the country. Therefore many patients who might benefit from this approach will never even be considered for potentially life saving treatment. BASO believes that NICE is uniquely positioned to influence and direct PCTs to increase the funding and hospital trusts to facilitate the expansion in liver surgery across the country to meet this predictable increase in demand. Secondly, knowledge of the literature published in this field before 2002 demonstrates that the degree of response of advanced CRC to oxaliplatin cannot be predicted (7-9). Therefore, even an extremely experienced liver surgeon (with considerable experience of the use of oxaliplatin) will miss patients with apparently hopeless disease who will in fact have a dramatic response to FOLFOX (and possibly irinotecan) and become resectable with curative intent.

1.7

In addition, it was clear even in 2001 that nearly 1 in 5 patients who were deemed unresectable on the basis of extra-hepatic disease, but came to resection after oxaliplatin based chemotherapy were alive five years after liver resection(9). Different surgeons apply different criteria to the definition of resectability with
curative intent (10), therefore NICE guidance 33 simply exacerbates a post-code lottery of possible treatments for these patients.

**What new evidence has emerged since 2002?**

2.1

By 2002 (and after the publication of NICE Guidance 33) it was clear that the original definition of resectability of colorectal liver metastases with curative intent (1-3 unilobar metastases, ideally presenting metachronously) was out of date and unacceptable (10). Adherence to this definition meant that less than 10% of patients could be considered suitable for surgery. It is now widely accepted by experienced liver surgeons that if the liver disease can be resected (even with a minimal or zero margin of healthy liver tissue) and as long as no more than 70% of the liver needs to be removed, then patients should be offered liver resection (10).

2.2

In the spring of 2003, the European Association for Research and Treatment of Cancer (EORTC) launched the CLOCC (Chemotherapy + Local ablation versus Chemotherapy) trial (EORTC 40004). In this trial, patients with advanced CRC whose disease is confined to the liver but considered inoperable with curative intent are randomised to receive FOLFOX in the control arm (regarded by the rest of Europe as the standard first line treatment of non-resectable advanced CRC) versus FOLFOX plus radiofrequency ablation (RFA) of their liver tumours. This trial has now recruited 70 of the 400 patients needed to complete the study.

2.3

Following the publication of NICE guidance 33 in 2002, further data emerged from Germany. These data showed the superiority of 5FU-leucovorin+oxaliplatin over the Mayo regimen of 5FU+leucovorin (11). In 2003, Rothenberg and colleagues (12) reported the therapeutic advantage of an oxaliplatin based regimen over an irinotecan based regimen in the treatment of patients with non-resectable advanced CRC. This study showed significant therapeutic advantage in response rate, time to progression and improvement in tumour related symptoms. By the time of the 2003 ASCO meeting, further trials from the US, Italy and Greece continued to confirm the statistically significant superiority of oxaliplatin and irinotecan based regimens over 5FU+folinic acid alone in the treatment of patients with advanced CRC with regard to response rates, survival and conversion of inoperable disease to resectability (13-16). This last report from a North Central Cancer Treatment Group (NCCTG) study (16) showing 14 of 42 (33%) previously unresectable patients coming to complete surgical resection of all residual tumour after response to oxaliplatin based chemotherapy. These patients were not selected for this study on the basis of possibly becoming resectable but reflected a general population of all-comers with non-resectable liver disease (personal communication, S R Alberts).

2.4
It is also now quite clear that if lung metastases of colorectal origin are resectable then five year survival following thoracotomy is commensurate with that seen after hepatectomy for colorectal liver metastases (17, 18). Variables that appear to independently predict long-term survival after thoracotomy include pre-thoracotomy carcino-embryonic antigen (CEA) levels, number of pulmonary tumours, the presence of hilar or mediastinal lymphadenopathy, histological grade of the primary colorectal tumour, the presence of extra-thoracic disease (17) and lung tumour size (18).

2.5

By early 2004, it was quite clear that people with advanced non-resectable colorectal cancer who received combination chemotherapy using 5-FU, leucovorin, oxaliplatin and irinotecan as first line therapy benefited in overall survival compared to those who received 5-FU+leucovorin alone (19). This meta-analysis of 7 recently published phase III trials in advanced CRC correlated the percentage of patients receiving second line chemotherapy (after the failure of first line) and the percentage of patients receiving all three agents with the reported median overall survival, using a weighted analysis. Crucially, (compared to present UK practice in which [if NICE guidance 33 is followed] patients must receive the now largely discredited 5FU+folinic acid regimens as first line therapy and when they progress, only 30% will receive proven more effective second line treatment) nearly 70% of patients in these studies received second line chemotherapy after failure of effective first line therapy using oxaliplatin and irinotecan based regimens.

2.6

The question of which of the two regimens (oxaliplatin versus irinotecan) might be the superior in first line therapy has been addressed by two studies published at the start of 2004. The first of these from an NCCTG study reported on a randomised controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic CRC (20). In this study, 795 patients were randomly assigned to receive irinotecan and bolus fluorouracil plus leucovorin (IFL), oxaliplatin and infused fluorouracil plus leucovorin (FOLFOX), or irinotecan and oxaliplatin (IROX). The study did not look at triple combination therapy using irinotecan with oxaliplatin and fluorouracil with leucovorin. The primary end point was time to disease progression after commencing chemotherapy and the secondary end points were response rate, survival time, and treatment toxicity. A median time to progression of 8.7 months, together with a response rate of 45% and median survival time of 19.5 months were observed for FOLFOX. These results were significantly better than those observed for IFL (time to progression 6.9 months, response rate 31%, overall survival 15 months) and IROX (time to progression 6.5 months, response rate 35%, overall survival 17.4 months) (18). The FOLFOX regimen achieved these better responses with significantly lower rates of drug related toxicity (20).

2.7

The relatively poor response to IROX should not be surprising in view of the relative inactivity of oxaliplatin when given without fluorouracil and leucovorin. Although reducing the dose of irinotecan in the IFL regimen can produce similar response rates
to higher dose IFL, the overall results are still not comparable to FOLFOX (21). Preliminary data from a randomised Phase III trial of 203 patients presented to ASCO in 2004 have suggested that the combination of oxaliplatin with irinotecan, fluorouracil and leucovorin (response rate 45%, disease stabilisation 32%, disease progression 23%, median time to progression 8.9 months, overall survival 21.1 months) is superior to a regimen of irinotecan, fluorouracil and leucovorin (response rate 31%, disease stabilisation 23%, disease progression 45%*, median time to progression 6.1 months, overall survival 16.5 months)(*p<0.05) (22).

2.8

Other trials presented at ASCO in the summer of 2004 have confirmed the benefits of oxaliplatin (23, 24, 25) and irinotecan (26) in first line therapy for advanced CRC. Overall response for combination oxaliplatin and capecitabine (CAPOX) in first line therapy was 50% with a median progression free survival of 16 weeks and median overall survival had not been reached at 31 weeks (23). Similar results were reported in both a Japanese study (24) and a Greek study (25) which also examined FOLFOX regimens. Combination therapy using capecitabine with irinotecan (XELIRI) was reported to achieve a 61% response rate with a median time to progression of 6.1 months and overall median survival of 15.6 months (26). Further data presented at the 2004 ASCO meeting have demonstrated that reducing the dose or frequency of administration of oxaliplatin based regimens can achieve equal efficacy as previously reported high dose regimens (27, 28). Similarly, good response with acceptable toxicity has been reported when capecitabine has been given with irinotecan as first line therapy in elderly (>65 years of age) patients with advanced CRC (29).

2.9

The second study to reach full publication at the start of 2004 (30) 220 randomly assigned patients with previously untreated advanced CRC with either a FOLFIRI regimen (line A) or FOLFOX6 (line B) (with variable infusion rates of leucovorin and fluorouracil). At progression of disease after commencement of chemotherapy, patients were switched to the other drug regimen as second line treatment. Of the 109 who were assigned to FOLFIRI as first line treatment, median survival was 21.5 months compared to 20.6 months for the 111 who received FOLFOX in first line (not significant). Median second line survival was 14.2 months in Line A and 10.9 in line B (not significant). Response rates to FOLFIRI in first line therapy were 56% with 8.5 month median progression free survival compared to 54% and 8.0 months after FOLFOX6 (not significant). Second line FOLFIRI achieved a 4% response rate and 2.5 months progression free survival compared to 15% and 4.2 months for second line FOLFOX6. However secondary surgery to remove previously inoperable metastases was performed in 10/109 patients (9%) after FOLFIRI compared to 24/111 patients (24%) who received FOLFOX6 (p=0.02). Secondary surgery to remove metastases after second line chemotherapy was possible in only a small number of patients (2 in line A and 1 in line B) (30).

2.10
A retrospective multi-centre study from France and presented at ASCO in 2004 reported on the long-term outcomes following liver resection in 56 patients who were initially unresectable but came to liver surgery after pre-treatment with various irinotecan based regimens (including 7 treated with both oxaliplatin and irinotecan) (31). The study did not describe the original denominator number of patients who were unresectable at the outset, and from which this numerator sample was derived. After a median follow-up of 15 months, the median overall survival after surgery was 34.2 months, with a 1 year survival rate of 92% and 2 year survival rate of 69%. Post-operative morbidity was moderately high at 37%, but operative mortality (<2 months) was acceptable at 3% and none was related to the chemotherapy treatment.

2.11

Lastly, data are now emerging on the impact on conversion of non-resectable liver metastases to operability by combination therapy using oxaliplatin with irinotecan, fluorouracil and leucovorin (FOLFIRINOX) (32). The primary end-point of the study was the attainment of resectability (R0 resection with margins ≥2 mm). The overall response rate after FOLFIRINOX in this small prospective French study of 34 patients was 72%. At the time of presentation (June 2004, ASCO), 25 patients were assessable for the primary end-point, and 22 of 24 assessable patients had came to surgery after FOLFIRINOX therapy. Of the patients who had come to surgery R0 resections were achieved in 9, R1 in 5, R2 in 6. Two patients had received cryotherapy instead of resection. Therefore 14 of 25 assessable patients had undergone potentially curative surgical resections.

Conclusions and recommendations of the British Association for Surgical Oncology to NICE on the Health Technology Re-appraisal on Guidance 33.

3.1

It is now quite clear that the 2002 NICE Health Technology Appraisal Guidance 33 (on the use of irinotecan, oxaliplatin and raltitrexed in patients with advanced colorectal cancer) was fundamentally flawed and has cost thousands of British patients with incurable cancer many months of high quality life. Furthermore, this guidance has denied a considerable number of these patients the opportunity to come to potentially life saving surgery.

3.2

This guidance has denied British patients with advanced colorectal cancer, the minimum standard of effective and appropriate treatment that has been readily available to their counterparts in the rest of Western Europe and the United States since 2000. As a consequence, there has been a failure by NHS planners (as reflected in the implementation of the NHS Cancer Plan) to appreciate the need for, and implementation of the appropriate expansion of liver cancer surgery services across the NHS. Indeed, in England where funding has been found within the cancer plan for an additional 500 consultants in cancer care, not one of these new posts has been for the creation of an additional consultant surgeon! This is at a time when 60% of patients cured of cancer are still cured by surgery alone.
3.3

The evidence on the use of irinotecan and oxaliplatin is now so overwhelming that (bearing in mind the paucity and weakness of evidence that still resulted in NICE recommendations to support the use of gemcitabine in pancreatic cancer, and glivec in leukaemia and gastrointestinal stromal cell tumours) the use of these drugs should be mandatory in first line treatment of advanced CRC. On balance it would appear that oxaliplatin has a therapeutic advantage when used as FOLFOX over irinotecan (19-22, 30), but it would appear from the emerging data that future advances in outcomes may lie in combination triple therapy which would employ both drugs in combination with 5-FU and folinic acid (32).

3.4

However, these recommendations will only be effective if the National Institute for Clinical Excellence recommends that hand in hand with their implementation, there is a redirection of the National Cancer Plan to specifically fund the expansion of liver cancer surgery (with the necessary infrastructure: anaesthetists, radiologists, intensivists etc.) within the established UK hepatobiliary surgery centres to realistically meet the increased surgical demand that such appropriate guidance will create.

References:

8. Giacchetti S, Itzhaki M, Gruia G et al. Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional


32. Quenet F, Nordlinger B, Rivoire M et al. Resection of previously unresectable liver metastases from colorectal cancer (LMCRC) after chemotherapy (CT) with CPT-11/L-OHP/LV5FU (Folfirinox): a