LEADING ARTICLE

Drugs 2005; 65 (14): 1935-1947
0012-6667/05/0014-1935/$39.95/0

Adjuvant Treatment Strategies for Early Colon Cancer

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Abstract

Colon cancer remains a major cause of death; however, in the last 3 years a number of trials have been published that have led to changes in the treatment of patients with this disease. Initially, the adjuvant treatment of patients following curative resection was based on their Dukes staging; this is now being refined by consideration of other pathological factors, as well as the investigation of newer prognostic markers such as p53, Ki67 and a number of genes on chromosome 18. Tumours generally develop from the progressive accumulation of genetic events, although some develop through mutation or inactivation of DNA mismatch repair proteins leading to microsatellite instability; this is particularly important in Lynch's syndrome. The loss of gene expression can occur by deletion or mutation of genes or by aberrant methylation of CpG islands.

In patients with Dukes C colon cancer the standard of care for adjuvant chemotherapy was previously based on bolus fluorouracil (5-fluorouracil) and folinic acid (leucovorin) administered 5 days per month or weekly for 6 months. Recent studies with a combination of infusional fluorouracil, folinic acid and oxaliplatin have been found to be superior. A further study replacing fluorouracil with oral capecitabine has also demonstrated equivalent disease-free survival. Although some debate remains regarding the benefit of adjuvant treatment for patients with Dukes B colon cancer, the emerging consensus is that, for those patients who are younger and have high-risk features, chemotherapy should be discussed. A number of large vaccine trials have also been conducted in the adjuvant setting and, overall, these have been disappointing.

This is a rapidly advancing area of therapy and the results of new trials are awaited to determine whether additional benefits can be achieved with biological therapies such as anti-vascular endothelial growth factor and anti-epithelial growth factor receptor monoclonal antibodies, which have already been shown to be effective in setting of metastatic colon cancer.

Colorectal cancer is a major cause of morbidity and mortality in the developed world. In the US it is the second most common cancer, with 106 000 people diagnosed with colon cancer in 2004 (American Cancer Society facts and figures[1]). The incidence in the UK was 35 300 in 2000, which is 13% of the cancer population (Cancer Research UK figures[2]). The majority of these patients have resectable tumours and, therefore, surgery remains the initial, potentially curative treatment option. The relapse rate is dependent on clinicopathological staging at surgery. Patients are staged according to the TNM

(Tumor size-lymph Nodes-Metastases) or Dukes systems. This clinicopathological staging is the most commonly used criterion to define the need for adjuvant chemotherapy. A number of large randomised trials have been conducted to examine the optimum adjuvant therapy and, more recently, trials have also examined which patients are likely to achieve most benefit from adjuvant chemotherapy following surgery. This review examines the evidence around both of these issues. Discussion is confined to the management of colon cancer, and rectal cancer is not included. The use of radiotherapy in conjunction with chemotherapy is common in rectal cancer and these diseases are usually considered separately for that reason. The role of radiotherapy is important in rectal cancers as the large intestine is fixed within the pelvic basin; however, the rest of the colon is a mobile organ with a number of important structures nearby, such as the liver and kidneys. It is difficult to treat patients with radiotherapy without toxicity to adjacent organs. Furthermore, in the majority of patients with colon cancer, relapse occurs in the liver and not locally. Consequently, unlike a number of other tumours, such as breast cancer, where radiotherapy is important in preventing local recurrence and is used as adjuvant therapy, there is limited value in giving radiotherapy for colon cancer in this setting. A recent review of literature on adjuvant radiotherapy in colon cancer suggested a benefit of locoregional radiotherapy for T4 N0-1 tumours, but the data for T3 N0-1 tumours were equivocal and this treatment is not recommended.[3]

1. Staging and Prognostic Markers

The majority of cancers that arise from the colon are adenocarcinomas. They are thought to develop through a multistep process of accumulation of genetic errors, leading to the development of hyperplasia followed by adenoma and then frank carcinoma.[4] Adenocarcinoma of the colon initially develops within the epithelium and is pathologically staged according to the degree of invasion through the intestinal wall. The Dukes classification proposed in 1932 is a simple pathological system, which was based on a group of rectal cancers that included palliative and radical surgical cases.[5] Dukes D is used to define those cancers that have distant metastatic spread. Table I defines the staging according to the Dukes classification and corresponding WHO TNM classification. Looking at the pathology of the tumour there are, however, other factors that are also implicated in the prognosis, such as lymphovascular invasion and invasion of the perineural sheath. In two large National Surgical Adjuvant Breast and Bowel Project (NSABP) trials, prognostic factors other than TNM staging were examined.[6] The site of the tumour was found to be of significant prognostic value, independent of staging. Tumours arising from the left colon had the most favourable prognosis, while rectosigmoid and rectal tumours had the worst outcome; the relative risk of treatment failure was 3-fold greater for

Table I. Staging classification for colon cancer

Dukes classification	Stage	Tumour	Description of tumour limit	Nodes	Description	Metastases
A	0	Tissue		N0		M0
	1	T1	Submucosa	N0		M0
		T2	Muscularis propria	N0		M0
B	II	T3	Subserosa, non-peritonealised pericolic tissues	N0		M0
		T4	Other organs or structures/ visceral peritoneum	N0		M0
C	III	Any tumour		N0		M0
		Any tumour		N1	≤3 regional	M0
		Any tumour		N2	>3 regional	M0
D	IV	Any tumour		Any node		M1

rectosigmoid and rectal tumours than for tumours of the left colon. Bowel obstruction was associated with a shorter disease-free survival (DFS) for patients with tumours on the right but not on the left side of the colon. However, when the gastrointestinal tumour study group examined tumour location and bowel obstruction they found that tumour location was not a significant prognostic factor, but that tumour obstruction, perforation and rectal bleeding were all poor prognostic factors.[7]

It is well established that lymph node status and resection margins are significant prognostic factors. The number of lymph nodes reported on in a pathological specimen is dependent on the surgeon adequately dissecting out the lymph nodes as well as the pathologist adequately displaying the mesentery. Wong et al.[8] examined 196 cases of colorectal cancer and found that at least 14 nodes needed to be recovered in order to give an accurate staging. Following on from this, a larger study was undertaken as part of the Intergroup Trial INT-0089 of patients receiving adjuvant chemotherapy.[9] The lymph node status of 3416 patients participating in the trial was examined and, as expected, the overall survival and DFS were reduced in those patients with increasing number of involved lymph nodes. However, interestingly, when they controlled for the number of lymph nodes involved, survival also increased with the total number of lymph nodes examined and this was even the case in the group of patients who had no involved nodes.[10] They concluded that a minimum of 18 lymph nodes needed to be examined to give a >25% probability of the staging being truly node-negative for T1 and T2 tumours and a minimum of ten nodes for the T3 and T4 tumours. A similar study, examining patients involved in the INT-0114 adjuvant trial, concluded that at least 14 nodes needed to be examined for staging to be adequate.[10] The consensus of members of the Cancer Committee of the College of American Pathologists suggests that 12 nodes need to be examined for adequate staging.[11] The paper also examined the consensus regarding other prognostic factors such as resection margins. Tumours have three resection margins that needed to be commented upon by the pathologist: the distal, proximal and circumferential radial margin. These margins are considered positive if there is evidence of macroscopic (R2) or microscopic (R1) disease at the margin. Patients have a better outcome if they have tumour-free margins (R0). Cell kinetics studies have shown that in patients with Dukes B and C tumours, the patients with diploid tumours survived longer. Furthermore, tumours with a high proliferation index, which is the number of tumour cells in the S and G2M phase of the cell cycle are associated with lower survival. In addition, in the majority of patients with colon cancer relapse occurs in the liver, not locally, and this is associated with a poorer prognosis.[12,13]

The advent of tumour markers such as carcinoembryonic antigen (CEA) has not only helped in the detection and monitoring of early development of tumour recurrence and metastasis but has also been explored as a potential prognostic indicator. In 358 patients with colorectal cancer who had a preoperative CEA level measured, a preoperative CEA level of >5 ng/mL was associated an increase in the recurrence rates for Dukes B and C tumours, and an inverse correlation was seen between CEA levels and the mean time to recurrence.[14] Therefore, the preoperative CEA level can further help to define patients into groups according to high or low risk of recurrence. Investigators examining the preoperative CEA levels in patients randomised to two large clinical trials of the NSABP found that preoperative CEA levels were a significant prognostic factor and independent of Dukes staging.[15] Therefore, when deciding on any further treatment, not only should the patient's TNM stage be considered but also other pathological features and preoperative CEA levels.

2. New Prognostic Indicators

Normal cell homeostasis is maintained by balancing cell proliferation with the deletion of aberrant or senescent cells by apoptosis. The development of cancer is due to the accumulation of genetic events that lead to the disruption of these mechanisms.[4] Therefore, a number of molecules involved in this process have been examined as potential prognostic indicators in colon cancer.[16] Genomic

instability can occur by the sequential inactivation of tumour-suppressor genes leading to transformation of the colonic epithelium through hyperplasia, dysplasia and cancer. Loss of genes such as the adenomatous polyposis coli (*APC*) gene,[16] found on chromosome 5q, p53 on chromosome 17p and the deleted in colon cancer (*DDC*), and *SMAD2* and *SMAD4* genes found on chromosome 18q are more frequently found in cells that have undergone these transformations.[17] Loss of heterozygosity at 18q has been found to be of prognostic significance in colon cancer.[18] Wild-type p53 is a transcription regulator at the G1 and G2 – M cell cycle checkpoints. It prevents the progression to S phase of cells with aberrant DNA, inducing apoptosis instead. Over-expression of p53 as a result of an increase in mutant p53 results in cell proliferation and the loss of apoptotic function as well as chromosomal instability. A number of studies have found that over-expression of p53 is associated with a more negative clinical outcome. However, there are also a few studies that do not agree with this conclusion and there may be a correlation between the site of the tumour (proximal vs distal) and the impact of p53 on the pathophysiology of the disease.[16,19-21]

Another prognostic factor that has been shown, at least in some studies, to affect outcomes is the proliferation marker Ki-67. After adjusting for the stage and grade of the cancer, Ki-67 was found to have a strong prognostic impact on overall survival and DFS. Interestingly, an increase in Ki-67 expression was associated with a better outcome. However, this was not necessarily due to an improvement in the response to chemotherapy.[16,21] Although the majority of tumours develop from an accumulation of genetic events and progress from hyperplasia to adenocarcinoma, around 15% of tumours develop through the mutation or inactivation of DNA mismatch repair (MMR) proteins. This leads to the insertion or deletion of nucleotides within repeated sequences of DNA, termed microsatellite instability (MSI). In 1997 the National Cancer Institute (NCI) recommended a panel of microsatellite markers to confer MSI. MSI-high is defined as two or more markers, MSS-stable is defined as the absence of these markers and MSI-low is an intermediate phenotype. Tumours with high levels of MSI are usually sporadic, have been found to metastasise less often and have a better prognosis than MSS cancers.[22] A number of syndromes that predispose to colon cancer have been examined to assess the importance of MSI. One such syndrome is hereditary non-polyposis coli, also known as Lynch's syndrome. Patients with this syndrome have a greater susceptibility to colon cancers as well as a number of other cancers (breast, skin, uroepithelial, endometrial, ovarian, gastric, biliary tract and prostate).[23] Between 30% and 80% of these patients have germline mutations in the following MMR genes: *MLH1*, *MSH2*, *MSH6* and *PMS2*.[24] This syndrome is dominantly inherited and, although in homozygous patients there is a reduction in MMR, there is no defect in DNA repair in heterozygous patients. However, if the wild-type allele is knocked out in the somatic cells of heterozygotes, such as the colonic epithelium, this leads to the development of cancer. This second hit can be due to deletion, mutation or methylation of CpG islands in the *MLH1* promoter. There are currently two NCI trials being conducted in the US examining the impact of MSI in patients with colon cancer. One trial is studying all patients and the second trial is examining younger patients aged 18–49 years. The investigators hope to evaluate the prognostic significance of MSI in both studies, and in the trial examining patients of all ages they wish to determine the significance of loss of heterozygosity for chromosomes associated with tumour progression (particularly chromosome 18).

Another molecular defect in sporadic colon cancer patients is aberrant methylation of cytosine within short sequences rich in CpG dinucleotides, known as CpG islands, found at the 5′ region of half of all human genomes.[25] Methylation of these regions leads to a loss of gene expression and is associated with the silencing of tumour suppressor genes in some cancers,[26] while global hypomethylation is seen in other cancers.[27,28] Studies in colon cancer have found an age-dependent increase in CpG island methylation in normal colon tissue. In colon cancer there was initially thought to be a particular CpG

island methylator phenotype (CIMP) with cancer-specific differentially methylated CpG islands.[29] However, the presence of two distinct groups of tumours, those with and those without a CIMP, has been disputed. Yamashita et al.,[30] using better techniques for examining these clones in cancer, showed that tumour-specific somatic hypermethylation was an age-dependent process that followed a normal gaussian distribution with a gradual change from tumours with a high frequency of CpG hypermethylation to tumours with a low frequency of hypermethylation. In the development of tumours, this methylation process precedes the development of MSI, as hypermethylation of CpG islands can lead to the silencing of the *MLH1* promoter that is involved in the development of MSI.[31] A number of other genes that are selectively downregulated by hypermethylation have also been identified in MSI-H cancers, such as *RAB32*, a Ras family member.[32] At present, these studies remain in the sphere of experimental work and clinical trials. In the meantime, the majority of clinicians use Dukes staging and pathological factors as the primary prognosticator.

3. Indicators of Chemosensitivity

Currently, the majority of patients with Dukes C colon cancer are given adjuvant chemotherapy that is based on fluorouracil (5-fluorouracil). However, we would still like to predict which of these patients will benefit from chemotherapy. Fluorouracil, upon conversion to its active metabolite 5-fluorodl-uridine monophosphate (UMP) irreversibly blocks thymidylate synthase. This enzyme is involved in the methylation of deoxy UMP to deoxythymidine-5′-phosphate in order to make thymidylate, which is a rate-limiting step for DNA synthesis. A number of studies have shown that thymidylate synthase levels correlate with the extent of fluorouracil resistance.[32] Another rate-limiting step in DNA synthesis is the pyrimidine catabolic pathway and high levels of dihydropyrimidine dehydrogenase are also associated with fluorouracil resistance. In 309 patients receiving adjuvant fluorouracil, the thymidylate synthase and DPD messenger RNA expression levels were predictors of survival: those patients with high thymidylate synthase levels survived longer, and in patients with high thymidylate synthase levels those with low DPD levels survived longer.[33] Other trials support this data and have found that patients with high tumour thymidylate synthase levels benefited from adjuvant fluorouracil-based chemotherapy.[34-36] Interestingly, in patients with metastatic colon cancer low levels of thymidylate synthase, thymidine phosphorylase or DPD were associated with a better response to chemotherapy and predicted improved survival.[37] Further trials are needed to see if patients with low thymidylate synthase and high DPD would benefit from alternative chemotherapy such as adjuvant irinotecan therapy.

4. Adjuvant Chemotherapy in Dukes C Colon Cancer

Prior to effective adjuvant treatment, patients with Dukes C carcinoma of the colon had a 60% risk of tumour recurrence. The majority of patients were treated with surgical resection only and initial studies did not show a significant survival benefit with adjuvant chemotherapy.[38] To address this situation, a large randomised multicentre trial (the United States Gastrointestinal Intergroup study 0035) was undertaken in 929 patients with potentially curatively resected Dukes C colon cancers.[39] Patients were assigned to observation alone, levamisole 50mg three times per day for 3 days every 2 weeks for 2 years or fluorouracil and levamisole, with the fluorouracil given at a dosage of 450 mg/m^2 of their body surface area daily for 5 days in every month. The initial results were published after 3 years and showed a 41% reduction in the recurrence rate in the fluorouracil and levamisole arm, with a reduction in the death rate of 33%. At 5 years the values remained the same, indicating that the benefit of chemotherapy was probably improving cure rates and not just increasing the time to relapse.[40] The rate of adverse effects seen in the fluorouracil and levamisole arm was similar to that seen with fluorouracil alone. The use of levamisole did not greatly impede patient compliance and there was no

convincing efficacy associated with this treatment, therefore this part of the regimen was dropped.

At the 1993 American Society of Clinical Oncology (ASCO) meeting, the results were presented of a study of adjuvant treatment of patients following potentially curative resection, which compared 6 months of observation with the same period of treatment with fluorouracil 425 mg/m^2 followed by low-dose folinic acid (leucovorin) 20 mg/m^2 for 5 days every 4 weeks.[41] The fluorouracil/folinic acid combination chemotherapy prevented relapse and there was an improvement in survival. The study was stopped prematurely as the observational arm was considered unethical in light of the findings of the Moertel et al.[40] study. The fluorouracil combined with folinic acid regimen (known as the MAYO regimen) became the standard of care for adjuvant treatment of Dukes C colon cancer, at least in the US. However, following the clinical response rate and reduction in toxicity of an infusional fluorouracil regimen in patients with metastatic colon cancer,[42] de Gramont's group[43] undertook a randomised study in 905 patients with Dukes C and B2 cancers. Patients received a MAYO-like regimen of folinic acid followed by fluorouracil 400 mg/m^2 for 5 consecutive days per month versus an infusional fluorouracil and folinic acid regimen for 24 or 36 weeks in a 2×2 factorial study. This study found that there were fewer adverse effects with the infusional fluorouracil and folinic acid regimen, that at the median follow up of 41 months there was no difference in DFS between regimens (73% vs 72%), and that overall survival at 3 years was 88% versus 86%.

There are other fluorouracil/folinic acid regimens that have also been used. The NSABP C-04 trial used a weekly regimen of fluorouracil and folinic acid, known as the Roswell Park regimen, to prove that fluorouracil and folinic acid was superior to fluorouracil and levamisole.[44] This regimen consists of weekly fluorouracil 500 mg/m^2 with high-dose folinic acid 500 mg/m^2 for 6 weeks followed by 2 weeks off for a total of 48 weeks. The trial in patients with Dukes B and C cancers had three arms: arm A, the Roswell Park regimen; arm B, weekly fluorouracil plus levamisole, as per the Intergroup 0035 study; and arm C, the Roswell Park regimen plus levamisole. Compared with fluorouracil and levamisole, fluorouracil and folinic acid showed an improvement in DFS at 5 years from 60% to 65% ($p = 0.04$) and an improvement in overall survival from 70% to 74% ($p = 0.07$). This fluorouracil and folinic acid regimen is widely used, although there has not been a direct randomised comparison with the MAYO regimen to determine which is more efficacious.

The MOSAIC (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) trial, recently updated at ASCO 2005[45] with a median follow-up of 4 years, randomly assigned 2246 patients to receive infusional fluorouracil and folinic acid alone or in combination with oxaliplatin. 279 (24.8%) patients in the fluorouracil plus folinic acid plus oxaliplatin regimen (known as the FOLFOX regimen) had a cancer-related event compared with 345 (30%) patients in the fluorouracil only group. This was a clinically significant difference with a hazard ratio of 0.77 and a p-value of 0.001, giving a 6.6% benefit for FOLFOX. In terms of toxicity, the incidence of febrile neutropaenia was 1.8% in the combination arm versus 0.2% in the fluorouracil arm. Grade 3 peripheral neuropathy, which is a common adverse effect of oxaliplatin, occurred in 12.5% of patients during treatment but had decreased to 0.5% after 18 months of follow-up. There was a greater frequency of gastrointestinal disturbances in the FOLFOX arm, but the majority were grade 1 and 2. The toxic death rate in each group was 0.5% with no difference between the arms.

A second study using a combination of fluorouracil and oxaliplatin was also presented at ASCO 2005.[46] The NSABP C-07 study used a fluorouracil regimen based on the Roswell Park regimen. 1207 patients in the control arm were treated with 500 mg/m^2 weekly bolus fluorouracil for 6 weeks and 500 mg/m^2 bolus folinic acid for 6 weeks in an 8-week cycle for a total of three cycles. In the treatment arm, 1200 patients were treated with the same regimen but with the addition of oxalipla-

tin 85 mg/m^2 on weeks 1, 3 and 5 of the 8-week cycle, for a total of three cycles. The DFS at 3 years was 76.5% for the treatment arm with the addition of oxaliplatin versus 71.6% for the control arm, which was significant ($p < 0.004$). This regimen also had a difference in neurotoxicity with 8% in the oxaliplatin arm and 1% in the control arm. The outcomes for these trials are considered by some authorities as too early for confident conclusions to be drawn. Certainly, most believe we need to await the 5-year data, including data on overall survival, which should be the definitive endpoint of any adjuvant trial. However, this long-held view has been examined formally by Sargent et al.[47] in order to enable comparisons of treatments in clinical trials to be translated more speedily into clinical practice. Sargent et al.[47] pooled data from 18 large randomised phase III trials of adjuvant colon cancer therapy with a sample size of 20 898 patients. They found that 2- and 3-year DFS correlated well with 5-year overall survival across trials; the correlations were 0.85 and 0.74 for median follow-up.

Further advances in the treatment of metastatic colon cancer have also occurred with another new chemotherapy agent, irinotecan, when used in combination with bolus fluorouracil and folinic acid as both first- and second-line treatments.[48] Therefore, a trial of 1264 patients treated with a bolus MAYO regimen alone or in combination with irinotecan was performed, known as the CALGB (Cancer and Leukaemia Group B) study 89803.[49] Surprisingly, this showed that there was no clinical benefit associated with the addition of irinotecan and that there was greater toxicity with a significantly greater frequency of treatment-related deaths (18 vs 6). A further study was conducted by the PETACC-3 (Pan European Trials in Adjuvant Colorectal Cancer) group comparing the de Gramont infusional fluorouracil egimen as standard, or in combination with irinotecan 180 mg/m^2. The results were disappointing, with a hazard ratio of 0.89 for 3-year DFS in favour of the irinotecan arm, which did not reach significance, in the Dukes C patients. For the pooled Dukes B/C patients the hazard ratio was 0.87 with a p-value of 0.038, which makes it a less appealing regimen than the combination of fluorouracil and oxaliplatin in the adjuvant setting, which gave hazard ratios of 0.76 and 0.77 for the two trials.[50]

As was shown by De Gramont and colleagues,[43] infusional fluorouracil for 6 months provides similar outcomes to bolus fluorouracil in the adjuvant setting. A recent study examined the effect of 6 months of adjuvant bolus fluorouracil/folinic acid, the Mayo regimen, in 404 patients and compared it with 3 months of protracted infusional fluorouracil 300 mg/m^2/day in 397 patients with Dukes B and C colon cancer.[51] They found there was no overall difference in survival between the two arms (71.5% in the bolus arm vs 73.3% in the infusional arm; hazard ratio 0.8, $p = 0.01$), with significantly less toxicity in the infusional arm. The paper discussed the likelihood that 3 months of infusional fluorouracil is probably not inferior to 6 months of bolus fluorouracil ($p = 0.005$) and that a shorter duration of adjuvant therapy may improve quality of life and, therefore, needs to be explored further in randomised trials.

Fluorouracil is one of the oldest chemotherapy agents used regularly in the treatment of cancer and, as previously discussed, has been part of the standard treatment for metastatic and adjuvant therapy for colon cancer for several decades. Capecitabine is an orally administered tumour-activated fluoropyrimidine. Capecitabine has activity in a number of cancers, including breast and colorectal cancer. In two large randomised trials comparing oral capecitabine with bolus fluorouracil and folinic acid (the MAYO regimen) in metastatic colon cancer, there were greater tumour response rates in the oral capecitabine group and time to disease progression and survival were equivalent.[52,53] Furthermore, capecitabine was better tolerated and more convenient to administer. Following this study, the capecitabine (Xeloda®)[1] in adjuvant colon cancer therapy (X-ACT [Xeloda Adjuvant Chemotherapy Trial]) study was performed, which has only been published in abstract form at ASCO 2005.[54] The adjuvant study again compared oral capecitabine to

1 The use of trade names is for product identification purposes only and does not imply endorsement.

the MAYO regimen. The primary endpoint of DFS at 3 years was 64.6% for capecitabine versus 61% for MAYO (hazard ratio of 0.87), which indicated equivalence of the capecitabine regimen to the MAYO regimen and also showed a strong trend towards the superiority of capecitabine. The trial showed overall survival of 81.7% with capecitabine vs 71.3% with fluorouracil, although the confidence interval crossed 1 and therefore capecitabine can not be considered superior. Capecitabine was better tolerated in general, with only hand foot syndrome being worse in the capecitabine group than the fluorouracil plus folinic acid group.

The XELOX (capecitabine plus oxaliplatin) trial in patients with metastatic colon cancer has recently been published.[55] The response rates, time to progression and survival data were similar to those for the FOLFOX regimen used in the MOSAIC trial. In light of this data, two trials are underway that compare capecitabine in combination with oxaliplatin to FOLFOX, both in the patients with metastatic disease and those undergoing adjuvant treatment. An alternative oral fluoropyrimidine, tegafur/uracil (UFT), is a 1 : 4 molar ratio of tegafur and uracil. This formulation was tested against a fluorouracil/folinic acid regimen in a US study, which was presented at ASCO 2004; equivalence was demonstrated between these regimens but it is unlikely this will alter practice (UFT is not licensed in the US).[56]

In the last 3 years two monoclonal antibodies have been found to be beneficial in the treatment of colon cancer. The first is bevacizumab, an anti-vascular endothelial growth factor antibody that has been found to give an additional survival benefit in the treatment of metastatic colon cancer when combined with irinotecan, bolus fluorouracil and folinic acid chemotherapy.[57] Following on from this data, trials are underway to determine whether bevacizumab has a benefit when used as adjuvant treatment in combination with FOLFOX or with capecitabine and oxaliplatin. A phase III clinical trial is underway to examine this (see table II).

The second monoclonal antibody is cetuximab, which binds to the epithelial growth factor receptor. Cetuximab has been found to give an additional benefit when combined with irinotecan in patients with disease that had previously progressed on irinotecan alone.[58] The role of cetuximab in the adjuvant setting remains to be elucidated, and the North Central Cancer Treatment Group (NCCTG)-N0147 study and a phase III clinical trial from the NCI hope to answer this question.

Table II. Randomisation of XELOX (capecitabine plus oxaliplatin) adjuvant trial[55]

Arms	Chemotherapy options	Bevacizumab option
A	Infusional FL + oxaliplatin	Bevacizumab
B	Infusional FL + oxaliplatin	Placebo
C	Capecitabine + oxaliplatin	Bevacizumab
D	Capecitabine + oxaliplatin	Placebo

FL = fluorouracil (5-fluorouracil) and folinic acid (leucovorin).

5. Relevance of Adjuvant Chemotherapy in Dukes B Colon Cancer

For patients with Dukes B staging who have no nodal disease the role of adjuvant chemotherapy remains hotly debated. A number of trials have now been published and much discussion has taken place to answer this question. The large clinical trials that have examined the role of adjuvant therapy following curative resection have often included a mix of patients with Dukes B and C cancers. Therefore, the studies have often been powered to indicate a clear survival advantage for patients with Dukes C colon cancer but have only been able to show trends for patients with Dukes B disease. Two trials treating patients with fluorouracil plus levamisole for colon and rectal cancers reported a separate analysis for patients with Dukes B cancer. For the subset of patients with Dukes B colon cancer in the NCCTG trial, no significant improvement in DFS or overall survival was reported with single-agent levamisole or combination levamisole plus fluorouracil compared with the observation arm.[59] In The Netherlands Adjuvant Colorectal Cancer Project, DFS and overall survival were improved in the fluorouracil plus levamisole arm compared with the observation arm for the patients with Dukes B colon cancer, with a relative survival benefit of 19% (SD ± 15); p-values were not reported.[60] The pooled data from

four NSABP trials, which grouped the best arms of each study compared with the worst arms of each study, showed benefit irrespective of stage.[61] This was further confirmed by pooling of adjuvant therapy data from seven randomised trials involving a total of 3304 patients with node-positive and -negative disease. On multivariant analysis, Gill et al.[62] found that there was a benefit through all subsets. However, the cure rate for patients with Dukes B disease is 70–80% without chemotherapy and there are adverse effects and a treatment-related mortality of 0.5–1% with the standard adjuvant treatments. Therefore, the benefit of subjecting these patients to adjuvant chemotherapy is questionable.

The IMPACT (International Multicentre Pooled Analysis of B2 Colon Cancer Trials) investigators examined five randomised controlled trials that allocated a total of 1025 patients to either observation or adjuvant fluorouracil-based chemotherapy treatment.[63] They found that survival at 5 years was 80% for the observed arm and 82% for the treatment arm and concluded that there was no additional benefit from adjuvant chemotherapy. The MOSAIC study, a more recent study that examined the addition of oxaliplatin to treatment with fluorouracil, found that, in the 40% of patients who were node-negative, FOLFOX was associated a hazard ratio for recurrence of 0.8 when compared with infusional fluorouracil; however, the 95% confidence interval crossed 1 (0.56, 1.15).[64] The authors used a Cox regression analysis to see if the benefit of adjuvant treatment differed between patients with Dukes B and C tumours and concluded that both groups of patients benefited from the oxaliplatin combination. The QUASAR (QUick And Simple And Reliable) study randomised 3238 patients to either bolus fluorouracil plus folinic acid in a modification of the MAYO regimen, a once-weekly regimen or observation.[65] Treatment efficacy did not differ significantly by stage, site, age or schedule. In the majority of patients who were node-negative there was a small (1–5%) benefit with chemotherapy. The QUASAR investigators recommended treating younger, higher-risk patients with Dukes B colon cancer, such as those with lymphovascular invasion. ASCO have recently published their recommendations on adjuvant chemotherapy for Dukes B colon cancer.[66] They conclude that there is no direct evidence from randomised controlled trials for the routine treatment of Dukes B colon cancer with adjuvant chemotherapy. However, they do state that, based on the benefit in patients with Dukes C disease, the indirect evidence of benefit in patients with Dukes B cancer may justify treatment of high-risk patients. There are further ongoing trials that may help to clarify this, particularly in the context of newer agents. The Eastern Co-Operative Group (ECOG) is presently undertaking an adjuvant trial assessing FOLFOX with or without bevacuzimab and plans to recruit 3000 node-negative patients. Those with favourable 18q (a prognostic marker) will be observed while the others will be treated.

Figure 1 shows a basic algorithm to help clinicians decide which category of patients may benefit from chemotherapy. However, there are no data to confirm that this group of patients respond better to chemotherapy and so have a survival advantage; rather, these risk factors marginally increase the risk of recurrence of the patients and, therefore, they have a greater benefit to risk ratio. This algorithm does not include the newer prognostic indicators, as trials to confirm the survival advantage from treating patients according to these markers are still awaited.

6. Adjuvant Immunotherapy

Immunology in colorectal cancer has had a difficult gestation. Immunology was initially thought to be potentially valuable as it was thought that the stimulation of the patients' immune system to react to and destroy antigens on tumour cells would be lifelong following vaccination and would help to prevent disease recurrence. A number of vaccine trials were undertaken in the late 1990s using autologous tumour cells linked to bacillus Calmette-Guerin in patients with Dukes B and C colon cancer who had undergone surgery. In some trials, vaccines were given in combination with chemotherapy,[67,68] while in others the vaccine was given alone.[69] In general, the combination with chemotherapy did not

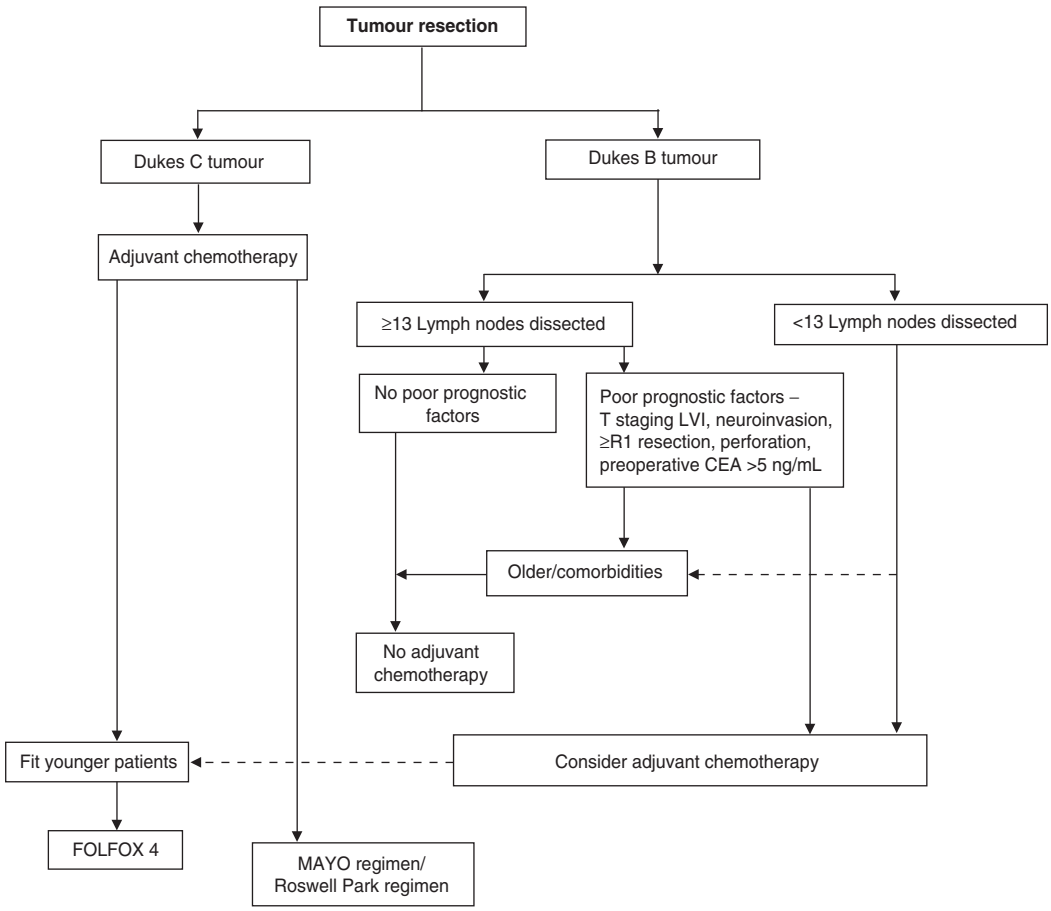

Fig. 1. Chemotherapy algorithm for adjuvant treatment. **CEA** = carcinoembryonic antigen; **FOLFOX** = oxaliplatin plus infusional fluorouracil/folinic acid (leucovorin); **LVI** = lymphovascular invasion.

show a survival benefit and the recent 10-year results of the NSABP protocol C-01, the largest trial involving 1166 patients who used semustine, vincristine and fluorouracil, which would no longer be used as adjuvant chemotherapy, with or without immunotherapy confirmed previous findings of no improvement in DFS or overall survival with the addition of immunotherapy. The phase II trial of immunotherapy alone published by Vermorken et al.[69] showed a longer recurrence-free period and a trend towards better overall survival in patients with Dukes B cancer treated with immunotherapy. A later analysis of this and two other phase III trials totalling 728 patients showed significant recurrence-free intervals, although these other two trials did not show any survival benefit.[70,71] There has been further preclinical work with dendritic vaccines using CEA as the antigen but results have been poor. At present, there is little evidence for the benefit of adjuvant immunotherapy in the treatment of colon cancer.

7. Conclusion

The treatment of colon cancer has developed rapidly in the last 5–10 years. In the past, the only treatment option for patients was surgery, but it is now well established that adjuvant chemotherapy provides an additional benefit for patients with Dukes C disease. Exciting new regimens employing

modern chemotherapy and biological agents are also being brought into the clinic.

A number of large randomised trials are still ongoing, which not only examine the optimum adjuvant therapies but also which patients will truly benefit from these treatments. In node-negative patients we would particularly like to identify those patients who are most likely to benefit from treatment by using a range of molecular markers to predict prognosis. Until then, the pros and cons of adjuvant chemotherapy should at least be discussed with node-negative patients who are young or at high risk of recurrence. For node-positive (Dukes C) patients it is a question of the optimum treatment. As yet, we do not know whether there is an additional benefit from treatment with small molecules. On the basis of the information presently available we would recommend the addition of oxaliplatin to infusional fluorouracil plus folinic acid (the FOLFOX regimen) for treatment of such cancers, particularly for young, fit patients (see algorithm, figure 1). At present in the UK, the National Institute for Clinical Excellence (NICE) guidelines only recommend FOLFOX for patients with resectable liver lesions. However, data from the large randomised MOSAIC trial show a benefit for patients with Dukes C colon cancer who are treated with FOLFOX. Since the majority of patients in the UK are treated under the National Health Service, until oxaliplatin chemotherapy is approved by NICE in this indication, clinicians in the UK are not at liberty to offer patients this regimen outside of the setting of a trial. Furthermore, the use of oral chemotherapy drugs such as capecitabine will mean a change in the way chemotherapy is administered and clinics are organised, with a greater emphasis on outreach and community involvement, which will benefit patients.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. The author has no conflicts of interest that are directly relevant to the content of this review.

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