Symposium article

Colorectal cancer in the adjuvant setting: perspectives on treatment and the role of prognostic factors

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In patients with stage III colorectal cancer (CRC) who have undergone potentially curative resection, adjuvant treatment with 6 months of 5-fluorouracil (5-FU) plus folinic acid (FA) is generally accepted as standard treatment and leads to a 5% to 10% improvement in absolute survival when compared with a no-chemotherapy control. In stage II CRC, the benefit of adjuvant chemotherapy has yet to be established. In metastatic CRC, randomized trials of irinotecan have consistently demonstrated that use of the drug, either alone or in combination with 5-FU/FA, prolongs survival. To investigate whether this benefit can be extended to patients with earlier disease, a series of multicenter trials are randomizing stage III colon cancer patients to adjuvant 5-FU/FA regimen with or without the addition of irinotecan. The role of adjuvant irinotecan is also being assessed in stage II colon cancer and in patients with rectal tumors. The risk/benefit ratio of adjuvant therapy in both stage III and stage II disease would be decreased if patients at the highest risk of relapse could be identified. Data from retrospective analyses suggest that DNA indexes, angiogenesis and some genetic/biological markers (loss of heterozygosity at chromosome 18 and the presence of microsatellite instability) identify prognostic differences in colon cancer patients. Their value as a guide to the intensity of adjuvant therapy required should be tested by randomized trial, as should the use of markers such as thymidilate synthase overexpression as a means of tailoring drug choice to tumor characteristics.

The current treatment of adjuvant colorectal cancer

Colorectal cancer (CRC) is one of the leading causes of cancer-related mortality in the Western world, and is responsible for around 400 000 deaths each year [1–3]. Approximately 30% of patients have advanced disease at presentation. Of the remainder, ~50% eventually relapse following potentially curative surgery. The need for effective chemotherapy in the adjuvant setting is therefore clear.

The most important pathological prognostic factor after surgery is disease stage, followed by the invasion of blood and/or lymphatic vessels, the number of locally involved lymph nodes and penetration or perforation of the bowel wall by tumor [4, 5]. The presence of penetration or perforation may be particularly important in defining the risk of patients with stage II disease. In addition to these pathological factors, aspects of tumor biology could in the future provide an important guide to likely outcome.

Among the sites of metastasis, the liver is the organ most frequently involved (in 38% to 60% of cases), followed by the abdominal lymph nodes (in 38%), the lung (38%) and peritoneum (28%) [5].

In the 1990s, several trials demonstrated that 5-fluorouracil (5-FU)-based regimens were effective in the adjuvant treatment of stage III (i.e. lymph node positive) CRC [6]. The use of bolus 5-FU plus leucovorin 5 days a month for 6 months is generally accepted as standard treatment and leads to a 5% to 10% improvement in absolute survival [3, 6]. This standard has evolved as a result of a number of key studies in this area, which are briefly reviewed.

Adjuvant trials in stage III disease

The Intergroup trial published in 1995 demonstrated that the use of 5-FU plus levamisole led to 60% 5-year survival [7]. Survival was 47% with surgery followed by no adjuvant chemotherapy, and 49% with surgery and adjuvant levamisole alone (Table 1).

This study was followed by the North Central Cancer Treatment Group–National Cancer Institute of Canada (NCCTG–NCIC) trial, in which 915 patients were randomized to 5-FU plus levamisole or 5-FU/FA plus levamisole for 6 or 12 months [8]. The results showed the benefit of adding folinic acid (FA) (75% overall survival compared with 63% in the non-FA arm). They also demonstrated that 12 months’ treatment did not confer additional benefit when compared with the shorter 6 month period of therapy.

In the Intergroup 0089 study, 3759 patients were randomized to one of four treatment arms: 5-FU plus levamisole, 5-FU plus high-dose FA, 5-FU plus low-dose FA and 5-FU plus low-dose FA plus levamisole [9]. The 67% 5-year overall survival seen in the 5-FU plus low-dose FA arm was not exceeded by any of the other regimens and was judged to be the preferred treatment (Table 2).

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In the QUASAR-1 study, 4927 patients were randomized to either 5-FU/FA or 5-FU/FA plus levamisole. The arm including levamisole had marginally worse 3-year survival (69.4% compared with 71.5% with 5-FU/FA alone; \( P = 0.06 \)). There was no survival difference between high- and low-dose FA regimens, and no difference according to whether 5-FU/FA was administered weekly or monthly. Recently, Sargent et al. [11] conducted a meta-analysis of seven phase III trials that had compared chemotherapy with surgery alone in stage II/III CRC. In five trials, 5-FU/FA was used, and in two trials 5-FU plus levamisole. The likelihood of recurrence-free survival was significantly higher in the chemotherapy group than in patients treated with surgery alone. Adjuvant treatment had a significant positive effect on both overall survival and time to tumor recurrence (\( P < 0.001 \) for each, with hazard ratios of death and recurrence of 0.76 and 0.68, respectively). While 64% of patients in the surgery arm of the trial were alive at 5 years, 71% of patients given additional chemotherapy survived to this point (\( P < 0.001 \)). The survival benefit in patients aged 70 years or more was similar to that seen in younger patients, and (with the exception of leukopenia in one study), age did not increase toxicity.

### Stage II CRC

The role of adjuvant chemotherapy in Dukes’ B (stage II) colon tumors is more controversial; however, a combination of chemotherapy and radiation therapy may be considered standard in rectal cancer. The role of adjuvant chemotherapy in stage II CRC remains to be defined by randomized clinical trials, and the current recommendation is that patients should be offered this treatment only in the context of such studies or, on occasion, to patients with high risk factors [12]. Petersen et al. [12] have demonstrated that the high risk factors in stage II disease are serosal involvement, extramural vascular invasion, involved resection margins and tumor perforation. The factors of undifferentiated tumors and age are not clear considerations.

The IMPACT B2 study involved a meta-analysis of data from 1016 patients involved in trials of adjuvant chemotherapy in stage II colon cancer [13]. The event-free 5-year survival in patients who had received 5-FU/FA was 76%, and that in the control arm 73% (\( P = 0.061 \)), while the figures for overall survival were 82% versus 80% (\( P = 0.057 \)). On this basis, it was argued that adjuvant chemotherapy should not be considered standard. However, it should be noted that the Dutch group’s recent study of 730 patients (half of whom had stage II disease) did suggest that adjuvant chemotherapy could improve relative survival in this group [14]. At a median follow-up of 4 years and 9 months, 78% of stage II patients treated for a year with adjuvant 5-FU/levamisole were alive, compared with 70% in the control arm (Table 3).

### The potential of new agents

While the situation in stage II CRC patients remains controversial, the benefit of adjuvant treatment in stage III disease is clear. It is hoped that the incorporation of new and highly active agents will further improve prospects for these patients. To gain clinical acceptance, the new agents will have to confer a survival advantage that is at least as great as that seen with the optimal intravenous 5-FU regimens.

Irinotecan holds promise in this area. As reviewed in detail in earlier papers in this volume, irinotecan has proven activity in patients with 5-FU-refractory disease and is recognized as standard treatment following 5-FU failure. Moreover, recent randomized trials have shown that the addition of irinotecan to 5-FU/FA improves response rate, time to progression and overall survival when compared with 5-FU/FA alone.

Treatment modalities with relatively low toxicity, such as tumorspecific immunotherapy involving antibodies or vaccines, may also have potential as adjuvant agents.

### The development of irinotecan in the adjuvant setting

Irinotecan is active in metastatic CRC, adds to the efficacy of 5-FU/FA, and can be given in combination with this regimen with a predictable and manageable profile of toxicities [15–19]. The
investigation of irinotecan in the adjuvant setting is therefore a logical progression.

There are currently three ongoing studies of adjuvant irinotecan in colon cancer. In the USA, the CALGB 89803 is comparing a Saltz arm (containing irinotecan + 5-FU) versus Rosewell Park 5-FU/FA alone.

In the phase III multicenter PETACC-3–EORTC trial, stage III patients are being randomized following surgery to either 5-FU/FA alone or 5-FU/FA plus irinotecan. In this instance, investigators can chose between the LV5FU2 regimen of de Gramont and the German Arbeitsgemeinschaft Internische Onkologie (AIO) schedule (Figure 1). In patients receiving the LV5FU2 regimen, irinotecan 180 mg/m² is administered over 30–90 min at the start of the period of FA infusion. In the case of patients treated with the AIO regimen, the dose of irinotecan is only 80 mg/m². Chemotherapy is given for 6 months. The primary end point of the study is 3-year disease-free survival among the stage III patients enrolled. Prognostic factors being evaluated in the study are thymidilate synthase (TS) expression, telomerase, loss of heterozygosity and microsatellite instability (MSI). Recruitment to the trial was ended in April 2002. In all, 2333 stage III patients have been enrolled.

In the French FNCLCC/FFCD trial, high-risk stage III patients are randomized to LV5FU2 or LV5FU2 plus irinotecan. High risk is defined as N2 disease with more than three positive nodes and N1 patients revealed by occlusion or perforation. Three year disease-free survival is again the primary endpoint. The 400 patients required have been accrued by September 2002 and final analysis is planned for 2004.

In addition to the three trials in colon cancer, the French AERO/GERCOR group is undertaking a study of adjuvant irinotecan in patients with rectal cancer. Patients (who may receive pre-operative but not post-operative radiotherapy) will be randomized to irinotecan plus LV5FU2 or to 5-FU/FA alone (delivered by either the Mayo Clinic or the de Gramont regimens). As of February 2002, 167 of the planned 600 stage II/III patients had been recruited.

Finally, the planned FFDC/EORTC/PETACC-4 study (due to start recruitment in mid-2002) aims to resolve certain issues surrounding the adjuvant treatment of patients with stage II disease. Patients with colon cancer, including that of the rectosigmoid junction, will be randomized either to surgery alone or surgery followed by irinotecan plus 5-FU/FA, given according to the de Gramont, AIO or TTD regimens. Biological prognostic markers will be studied in parallel.

**Biological prognostic factors**

Of CRC patients, 50% are cured by surgery alone [20]. The survival data from the controlled adjuvant therapy trials discussed above suggest that ~7% of patients who would otherwise relapse are cured by post-surgical chemotherapy. The corollary of this is that 43% are not.

Identifying the patients who belong to each group would enable efforts to be concentrated on those most in need of chemotherapy, while those unlikely to benefit could be spared the toxicities of treatment. The first steps towards assigning adjuvant therapy according to the molecular characteristics of the specific tumor are now being taken.

Among stage III CRC patients treated adjuvantly with 5-FU-based combinations, Watanabe and colleagues identified three molecular factors related to survival [21]. Loss of heterozygosity at chromosome 18q was associated with poor prognosis, while the presence of MSI and mutation of transforming growth factor-β were associated with a favorable outcome. Combining these three factors identified two groups of patients with substantially different prognoses.

**Microsatellite instability**

The Finnish group of Hemminki et al. [22] had previously identified the presence of MSI as a favorable factor in CRC patients receiving chemotherapy. In their series of patients treated with adjuvant 5-FU based regimens, 90% of MSI-positive patients

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**Figure 1. International Adjuvant Trial Treatment/PETACC-3: treatment schema.**
were recurrence free at 4 years, while this was true of only 43% of patients without MSI.

Elsaleh et al. [23] also identified an interaction between chemotherapy and MSI status in a retrospective study in stage III patients. Among patients not treated with adjuvant chemotherapy, the presence or absence of MSI made no difference to survival. However, when chemotherapy was administered, the presence of MSI seemed to confer highly significant survival advantage. The PETACC-3 trial is prospectively analyzing MSI status.

In an ongoing initiative, the Mayo Clinic, NCIC and the IMPACT group are retrospectively assessing the role of MSI status in a total of 1200 adjuvant patients. In a preliminary report at the last American Society for Clinical Oncology (ASCO) meeting, data on 570 tissue specimens confirmed that patients with high frequency MSI (MSI-H) have a better survival compared with patients with microsatellite stable (MSS) tumors. This advantage, however, was lost in the presence of chemotherapy. Adjuvant chemotherapy was found to have a beneficial effect in patients with MSS tumors but in patients with MSI-H tumors it predicted a worse outcome. These data, although preliminary, seem to suggest that adjuvant chemotherapy is not warranted in patients with MSI-H tumors, since it may even be detrimental [24].

However, the study by Barratt et al. [25] showed that retention of heterozygosity at one or more microsatellites within the p53 gene on 17p or on 18q was associated with the ability to benefit from adjuvant fluorouracil therapy. The benefit of chemotherapy in this subset of patients was striking, with a hazard ratio of 0.45 (95% confidence interval 0.28–0.73).

### Markers of angiogenesis and proliferation

The presence of molecular or biological markers of angiogenesis or proliferation may also be relevant to metastatic potential.

Cascinu et al. [26] recently investigated vascular endothelial growth factor (VEGF) expression and the S-phase fraction of tumors in node-positive patients with and without relapse following adjuvant chemotherapy. Relapsed patients were further divided into those relapsing before or after 12 months.

The majority of patients without relapse (69 from a total of 94) had tumors with a low S-phase fraction and low VEGF expression (Table 4). All but one of the patients with early relapse had tumors that were both high in S-phase fraction and VEGF positive, while those who relapsed late had tumors high on either the proliferation or the angiogenesis marker. Since they are retrospective, these data should be treated with caution. However, they are sufficient to suggest the prognostic significance of biological and molecular parameters within stage III disease.

<table>
<thead>
<tr>
<th>No relapse</th>
<th>Early relapse</th>
<th>Late relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>High SPF-positive VEGF</td>
<td>Low SPF-positive VEGF</td>
<td>High SPF-negative VEGF</td>
</tr>
<tr>
<td>21</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>27</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>0</td>
<td>13</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 4. Analysis of VEGF and SPF in patients with and without relapse [26]

Table 5. Stage II CRC patients with overexpression of marker of angiogenesis

<table>
<thead>
<tr>
<th>Author [Ref.]</th>
<th>Parameter</th>
<th>No. of patients</th>
<th>Prognostic factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takahashi [31]</td>
<td>Factor VIII</td>
<td>27</td>
<td>Yes</td>
</tr>
<tr>
<td>Banner [32]</td>
<td>Factor VIII</td>
<td>101</td>
<td>Yes</td>
</tr>
<tr>
<td>Cascinu [33]</td>
<td>VEGF</td>
<td>121</td>
<td>Yes</td>
</tr>
</tbody>
</table>

VEGF, vascular endothelial growth factor; SPF, S-phase fraction.

Such work may eventually enable us reliably to distinguish between patients with a low risk of relapse requiring no (or only low-dose) adjuvant therapy and those at high risk requiring intensive or combination treatments.

### Tailoring drug choice

Markers also have the potential to optimize therapy by tailoring the drug used to measures of likely sensitivity or resistance. There is already evidence that TS may be helpful in this context [27, 28]. In a series of 100 patients treated with adjuvant 5-FU, all but four of the 30 patients who relapsed were TS positive [26]. Of those remaining disease free, 48 (67%) were TS negative. Patients with tumors overexpressing TS may therefore not be good candidates for 5-FU, but could have an improved outcome if treated with agents with a different mechanism of action.

### Prognostic markers in stage II disease

The adjuvant therapy of stage II CRC is not widely accepted. However, attempts have been made to identify the 20% of B2 patients likely to experience recurrence. Tumor perforation or adherance, the invasion of adjacent organs and poor differentiation could all be considered risk factors. Biological and molecular markers are also likely to play a part in predicting relapse.

Along with other groups, Cascinu et al. [29] have found that use of an index based on S-phase fraction can predict event-free survival in patients with pT2-T3–N0–M0 disease. Stage B patients high on this marker for proliferative activity appear to have the same risk of recurrence as those with stage C disease. This is also true for B2 stage patients subsequently shown by PCR analysis of lymph nodes to have micrometastases [30].

As in stage III disease, stage II patients whose tumors overexpress the VEGF marker of angiogenesis also fare less well than patients who are VEGF negative on immunostaining (Table 5) [31–33].
These data clearly provide the grounds for further work. It is not yet justified to individualize adjuvant treatment to the tumor characteristics evident in a particular patient. However, biological and molecular studies carried out as an integral part of prospective molecular studies will hopefully soon provide the justification for such an approach.

Disclosure

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