Adjuvant treatment in Dukes’ B and C disease

Jacques A. Wils

Laurentius Hospital, Department of Oncology, Roermond, The Netherlands

Introduction

Colorectal cancer is a leading cause of morbidity and mortality, with approximately 300,000 new cases and 200,000 related deaths in Europe and the USA each year [1]. Up until 1988, the vast majority of oncologists considered adjuvant chemotherapy for colorectal cancer to be of no advantage since the results of different randomised studies failed to demonstrate any therapeutic benefit. Subsequent trials, however, led to the general acceptance of adjuvant chemotherapy in Dukes’ C colon cancer.

In rectal cancer adjuvant treatment modalities in North America and Europe are different. Current results will be discussed and strategies for the future will be outlined, including on-going or planned large-scale trials with new drugs and approaches.

Adjuvant treatment of colon cancer

In 1988 and 1989, two large cooperative group trials showed a significant benefit for adjuvant chemotherapy in colon cancer [2,3]. Opinion on the usefulness of adjuvant chemotherapy changed definitively when the results of the Intergroup study from the USA became available [4], although conflicting views were taken by European oncologists whose initial response was more conservative [5]. In the meantime, the 6.5-year results of the Intergroup trial were published with the same conclusions as those made in the original publication [6].

The evidence that adjuvant therapy is effective in colon cancer was further confirmed by two controlled studies that compared 5-fluorouracil/leucovorin (5-FU/LV) treatment with control for six [7] or 12 months [8]. In addition, the pooled six-months results of three trials of 5-FU/LV showed significant increases in three-year event-free and overall survival in comparison with a control [9]. In a subsequent study (C-03) conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), a significant survival benefit was reported for 5-FU/LV compared to MOF (methyl-CCNU, vincristine [Oncovin] and 5-FU) with equal benefit in stages B and C [10]. The prolonged disease-free and overall survival obtained with 5-FU/LV in these trials appeared to be of the same magnitude as that obtained with 5-FU/levamisole in the Intergroup study. As a consequence of these studies, the evidence that systemic adjuvant 5-FU-based treatment can delay or reduce recurrence after resection of high-risk (Dukes’ C or TNM stage III) colon cancer is now compelling and generally accepted.

The question about the exact nature of the pharmacological interaction between 5-FU and levamisole has become less vexing now that equally or even more effective regimens have become available [11]. Results from two large-scale USA studies (Intergroup 0089 and NSABP C-04), in which 5-FU/LV and 5-FU/levamisole, plus the combination of the three drugs, were compared in over 5600 patients, did not reveal significant differences among the regimens. The NSABP trial indicated a disease-free survival advantage for 5-FU/LV over 5-FU/levamisole [12], while the four arms Intergroup trial did not show relevant differences among the five planned comparisons. Although 5-FU plus low-dose LV (LDLV)/levamisole was significantly superior to 5-FU/levamisole, it was not superior to 5-FU/LDLV alone [13]. Furthermore, six months of treatment with 5-FU/LV does not appear to be inferior to 12 months of treatment [14]. NSABP study C-05 compared FU/LDLV with the same combination plus interferon. No differences, except in toxicity profiles, were reported [15].

In conclusion, it can be argued that 5-FU plus either high-dose (weekly or 'RoswelF regimen) or low-dose LV (monthly or 'Mayo regimen') for 6 months is currently the most widely accepted 'standard' treatment in colon cancer.

Other trials in this area are ongoing, including the Mid-Atlantic Oncology Program (MAOP) study, comparing infusional with bolus 5-FU programs, and Intergroup study S 9415 that is evaluating protracted infusional 5-FU plus levamisole versus bolus...
5-FU/LV and levamisole. Two international trials in which the monoclonal antibody 17-1A (Panorex) plus FU/LV is being compared with antibody alone and/or FU/LV have completed accrual.

**Adjuvant treatment of stage II colon cancer**

In stage II colon cancer, adjuvant treatment is controversial and not generally accepted [16,17]. Available data do not show a clear benefit and further research is needed [18]. Specific immunotherapy might have an impact in this stage of the disease and one study with only 254 patients reported significant prolongation of progression-free survival in 170 patients with Dukes’ stage B colon cancer [19]. A study with monoclonal antibody 17-1A versus control in this stage of disease is still ongoing. This trial was initiated by the CALGB (Cancer and Leukemia Group B) and will be possibly be joined by different groups in Europe.

Attempts have been made to identify B2 patients at high risk of recurrence. Several characteristics such as tumour perforation, tumour adherence, invasion of adjacent organs, poorly differentiated tumours, venous or lymphatic invasion or perineural invasion could be considered as high-risk factors.

A potential other approach is the detection of micro metastases using the reverse transcriptase polymerase chain reaction (RT–PCR) assay for carcinoembryonic antigen (CEA) messenger RNA (mRNA) [20].

Multilevel microsections of sentinel lymph nodes identified at operation as the first 1–3 blue nodes identified within the first 5 minutes after subserosal injection of 1 ml 1% lymphazurin around the tumour, showed micro metastases in 17.5% of patients who had no lymph node involvement on standard examination [21].

The thymidylate synthase (TS) as well as dihydropyrimidine dehydrogenase (DPD) expression levels inversely correlate with sensitivity and response to 5-FU both in vitro [22] and in vivo [23–25]. It could also be of prognostic value in the adjuvant setting [26]. The use of RT–PCR measurement could further improve the sensitivity of the method [27] and its capability for identifying those Dukes’ B2 patients at risk of recurrence.

**Portal-vein infusion**

Portal-vein infusion (PVI) of cytotoxic drugs is another method of adjuvant treatment that was popularised at the University of Liverpool, UK [28]. However, results of different randomised studies that attempted to confirm the initial positive data were inconsistent. A meta-analysis has been performed on the updated results of nine completed 'confirmatory' trials with adjuvant PVI. Results from 4437 patients show a small but significant survival benefit with therapy (annual death risk reduction 11 ± 5%, \( p = 0.04 \); absolute increase in 5-year survival 3.6%, \( p = 0.04 \)), but no effect on the incidence of liver metastases [29]. Two recently completed, large studies from the EORTC and one from the UK (Adjuvant X-ray and Infusion Study), however, do not show a benefit from intraportal infusion versus observation [30,31]. Moreover, when the results of the EORTC trial are added to the meta-analysis, the annual reduction in death rate is no longer significant (8 ± 5%; \( p = 0.10 \)).

It has been suggested that the apparent benefit from PVI might result from a systemic effect, particularly by the timing of chemotherapy. However, the results of a trial conducted by the SAKK, where perioperative systemic chemotherapy was compared with PVI and a control do not show any benefit for PVI or short-term perioperative systemic treatment [32]. The conclusion after 10 years of clinical investigation is almost inevitable: there is no longer a role for PVI and the concept of intraportal short-term adjuvant chemotherapy should be abandoned.

Whether any benefit can be obtained from the combination of early perioperative intraportal treatment plus standard systemic chemotherapy is a question that has been assessed by the EORTC Gastrointestinal Tract Cancer Cooperative Group (GITCCG) and by a similar study in Italy (Studio Multicentrico Adiuvante Colon [SMAC]). Results from the SMAC trial do not show a benefit for the combined approach [33]. Data from the closed EORTC trial which was conducted in cooperation with the Fondation Française de Cancérologie Digestive (FFDC) and was initiated in 1993 and recruited \( \approx1800 \) patients, are not yet available. Early postoperative treatment was administered via either the intraportal or intraperitoneal route, dependent on the institution's experience. Systemic chemotherapy was either 'standard' 5-FU/levamisole or 5-FU plus L-leucovorin, both of which were administered for six months. In the USA, Intergroup study INT 136 is comparing perioperative systemic 5-FU infusion followed by 'standard' 5-FU/LV versus 5-FU/LV alone. However, it does not appear likely that either of these two studies will produce any new perspectives.
International cooperation in Europe

Adjuvant trials consume a considerable amount of time, especially in Europe. Investigators can contribute more effectively to the progress of adjuvant treatment in colorectal cancer by entering patients into large-scale cooperative trials. For example, in the recently initiated Pan European Trials in Adjuvant Colon Cancer (PETACC) structure, different national groups are participating in cooperative studies, the aim of which is to randomize large numbers of patients in 1 to 2 years. In the first two trials, standard bolus 5-FU plus LV ("Mayo schedule") is being compared with raltitrexed ("Tomudex") (PETACC-1) or high-dose infusional 5-FU (PETACC-2) [34].

After randomisation of 1835 patients within 15 months, unfortunately, PETACC-1 was closed by the sponsor Astra-Zeneca to further randomisation before the target accrual of 2800 patients. The reason for this action was that the independent data monitoring committee (IDMC) had recommended a temporary suspension of recruitment due to an excess of drug-related fatalities in the "Tomudex" arm. The IDMC also recommended that a further safety and efficacy evaluation should be carried out. The PETACC Steering Committee agreed to follow these recommendations. The sponsor, however, after having taken an unscheduled review of 'interim' efficacy data, which were not seen by either the IDMC or the Steering Committee, decided to close the trial. As a result, the true benefit or lack of benefit of raltitrexed will become difficult if not impossible to assess.

A second study, PETACC-2, continues to be carried out to compare the Mayo regimen (5-FU 370 or 425 mg/m² plus leucovorin 20 mg/m² for 5 days every 4 weeks for 6 cycles) with 3 high-dose infusional 5-FU regimens. Most studies comparing infusional 5-FU ± LV with modulated bolus regimens have shown a higher response rate, a safe toxicity profile and a trend for superior survival. Three infusion regimens (24 hours weekly HD-FU/LV, 48 hours weekly HD-FU and 48 hours biweekly infusional FU/LV) are being assessed in the infusion arm of the trial; these regimens have not been directly compared, but the assumption is that no major differences exist.

A second study, PETACC-2, continues to be carried out to compare the Mayo regimen (5-FU 370 or 425 mg/m² plus leucovorin 20 mg/m² for 5 days every 4 weeks for 6 cycles) with 3 high-dose infusional 5-FU regimens. Most studies comparing infusional 5-FU ± LV with modulated bolus regimens have shown a higher response rate, a safe toxicity profile and a trend for superior survival. Three infusion regimens (24 hours weekly HD-FU/LV, 48 hours weekly HD-FU and 48 hours biweekly infusional FU/LV) are being assessed in the infusion arm of the trial; these regimens have not been directly compared, but the assumption is that no major differences exist.

New drugs for the treatment of advanced colorectal cancer are now available and in the coming years much efforts will undoubtedly be given to assess these drugs in the adjuvant setting. Among the new agents are the oral FU prodrugs such as UFT (tegafur + uracil), oral 5-FU + enyluracil, capecitabine and UFT + LV ("Orzel"). The NSABP has closed a trial (C-06) that compared Orzel with FU/LV and results are awaited. A company conducted trial in which capecitabine is being compared with bolus 5-FU/LV has recently been initiated.

Other trials with new agents

Additionally, irinotecan and oxaliplatin have different mechanisms of action compared to 5-FU and several studies have added weight supporting their emerging role in combination therapy particularly for advanced disease [35-37] as well as in 5-FU resistant patients [38]. These drugs will now be tested in the adjuvant setting in the USA and Europe mainly in combination with FU/LV versus FU/LV alone. In Europe an Aventis-sponsored trial will compare infusional 5-FU (using a choice of two regimens) with or without irinotecan. This study will possibly be run in cooperation with the PETACC framework.

In the UK a trial will be launched that compares bolus FU/LV ± CPT-11 with capecitabine ± CPT-11. Another trial, sponsored by Sanofi-Synthelabo, will compare biweekly infusional FU/LV with the same regimen plus oxaliplatin ("Mozaïc" trial). In the USA Intergroup and NSABP will conduct trials assessing the addition of CPT-11 or oxaliplatin to bolus 5-FU/LV. In Table 1 a summary of relevant trials is shown.

An additional challenge is to determine the means by which physicians can individually tailor new therapies, i.e. select new agents, either as monotherapy or in combination, as best treatment on the basis of individual patients' biological markers (thymidylate synthase expression, RT-PCR assay, topoisomerase-1 gene expression, p53 status etc.).

Adjuvant treatment of rectal cancer

In a clinical announcement published in March 1991, the National Cancer Institute (NCI) stated that combined modality treatment with a sequential regimen of 5-FU-based chemotherapy and postoperative irradiation concurrently with 5-FU may be recommended as therapy for individuals with resected TNM stage II and III cancer. This statement was based on results that had emerged from randomised trials in the USA showing significant benefit in reduction of local recurrence rate and survival for postoperative combined modality treatment [39-41].

The role of adjuvant chemotherapy was addressed by a study conducted by the NSABP [39]. Congruent with their results in colon cancer, chemotherapy led to a survival advantage ($p = 0.05$) over radiotherapy
Table 1
Summary of relevant ongoing or planned trials

<table>
<thead>
<tr>
<th>Group/Company</th>
<th>Control arm</th>
<th>Experimental arm</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>PETACC-1</td>
<td>Bolus FU/LV</td>
<td>Tomudex</td>
<td>Premature closure</td>
</tr>
<tr>
<td>PETACC-2</td>
<td>Bolus FU/LV</td>
<td>Infusional FU ± LV</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Aventis</td>
<td>Infusional FU/LV</td>
<td>Inf FU/LV + CPT-11</td>
<td>To be launched</td>
</tr>
<tr>
<td>Sanofi-Synthelab</td>
<td>Infusional FU/LV</td>
<td>Inf FU/LV + oxalipl</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Roche</td>
<td>Bolus FU/LV</td>
<td>Cepetabine</td>
<td>Ongoing</td>
</tr>
<tr>
<td>QUASAR-2</td>
<td>Bolus FU/LV</td>
<td>FU/LV + CPT-11</td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cepetabine + CPT-11</td>
<td>To be launched</td>
</tr>
<tr>
<td>NSABP C-06</td>
<td>Bolus FU/LV</td>
<td>Orzef</td>
<td>Closed</td>
</tr>
<tr>
<td>NSABP C-07</td>
<td>Bolus FU/LV</td>
<td>Bolus FU/LV + oxalipl</td>
<td>To be launched</td>
</tr>
<tr>
<td>Intergroup</td>
<td>Bolus FU/LV</td>
<td>Bolus FU/LV + CPT-11</td>
<td>To be launched</td>
</tr>
<tr>
<td>Glaxo/Wellcome</td>
<td>Bolus FU/LV</td>
<td>Bolus FU/LV + Panorex</td>
<td>Closed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Panorex</td>
<td></td>
</tr>
</tbody>
</table>

and control. It should be noted, however, that this study did not include a combined treatment arm and that there was no improvement in local tumour control with chemotherapy only.

The combined application of chemotherapy (methyl-CCNU plus 5-FU) with irradiation was assessed by the Gastrointestinal Tumor Study Group (GITSG) and resulted in 24% improvement in the seven-year survival in the combined modality approach compared with control ($p = 0.005$) [40,42]. There was no significant survival advantage for the combined modality over irradiation alone. A second study, which favoured the combined approach, was conducted by the Mayo Clinics/North Central Cancer Treatment Group (NCCTG). This trial yielded a significant survival benefit for combined modality treatment over irradiation alone [41], but it is important to note that this trial contained neither a chemotherapy-alone arm nor a control arm.

Chemotherapy in the NCCTG/Intergroup study (NCCTG 864751), which accrued 660 eligible patients, consisted of different schedules of 5-FU concurrent with postoperative irradiation and 5-FU plus or minus methyl-CCNU before and after radiotherapy. After a median follow-up of 46 months, results showed superior survival for continuous infusion 5-FU as opposed to bolus injections during radiotherapy ($p = 0.005$). This advantage resulted mainly from a decrease in distant relapses [43]. This study importantly showed a survival advantage for infusional 5-FU over bolus injections. These results and data from another study [44], furthermore, demonstrated that methyl-CCNU should be omitted and suggest that continuous infusion of 5-FU combined with postoperative radiotherapy is an effective treatment, but do not prove an additional survival benefit of radiotherapy.

Is that all there is? The first GITSG study is the only one that has demonstrated superiority with combined modality treatment over surgery alone. However, one could argue that it is difficult to accept that a substantial benefit can be derived from a chemotherapy protocol that is deferred for more than two months after surgery, that is not received by 15% of patients, and that contains a drug subsequently shown to be of no therapeutic value or even to be detrimental. Although the Mayo Clinics/NCCTG trial showed a significant survival benefit for chemono-irradiation over irradiation and was well designed, it did not contain a chemotherapy-alone arm. Furthermore, reports of late radiotherapy-related serious toxicity are of concern; the percentage of patients suffering from these sequelae has to be weighed against the percentage that enjoys potential survival benefit.

Other trials from the USA include the NSABP R-02 study which compared chemotherapy programs (MOF or leucovorin plus 5-FU) with chemotherapy plus irradiation [45]. There were no differences in three-year disease-free and overall survival between patients who received chemotherapy alone versus those who received additional radiotherapy. However, in patients randomised to the radiotherapy arms, there was a small but significant reduction in local recurrence at the site of first treatment failure. Intergroup (Mayo Clinics/NCCCTG, CALGB, ECOG, SWOG, RTOG and NCIC) study 0114 incorporated irradiation in all four protocol arms and compared different chemotherapy protocols. It utilised sequential single agent 5-FU and high-dose pelvic irradiation plus concurrent bolus injections of 5-FU as the control group, while the experimental groups employed combinations of 5-FU, levamisole and LV plus radiotherapy. With 1696 patients randomised and four years of follow-up, there were no significant advantages for any
of the experimental arms compared with the standard arm, although the 5-FU/LV arm might show some benefit with longer follow-up. In addition, the three-drug regimen was more toxic [46]. The subsequent Intergroup study INT 0144 employs radiation with infusional 5-FU or bolus 5-FU/LV/levamisole, preceded and followed by bolus 5-FU, infusional 5-FU or bolus 5-FU/LV/levamisole. This study will provide additional important information about optimal ways of administering 5-FU in the adjuvant setting.

In Europe, the recommendation made by the NCI has never been adopted [47]. Although radiotherapy is considered by many to be the adjuvant treatment of choice, at least in patients at high risk for local recurrence, European investigators, especially from Scandinavia, have advocated preoperative intensive short courses of irradiation (500 cGy x 5) [48,49]. One trial even showed a survival benefit [49]. Points of concern with this approach, however, are the lack of specific methods to identify high risk patients preoperatively (therefore, early stages can be 'over-treated'), down-staging (resulting in cessation of potentially beneficial post-operative chemotherapy), no enhancement in the percentage of patients who can undergo sphincter preservation [as opposed to conventional (5040 cGy) six-week preoperative standard irradiation], and increased toxicity. Furthermore, combined modality treatment could be more effective than radiotherapy alone, and with irradiation consisting of 25 Gy in five days, this combined approach will probably be very toxic [50]. Randomised trials comparing pre- and post-operative conventional irradiation plus concurrent chemotherapy in resectable T3 stage are ongoing (NSABP trial R-03; German trial) but suffer from insufficient accrual.

Therefore, in contrast to the NCI's recommendations, many European investigators feel that it is premature to advocate combined modality as routine treatment outside the clinical trial setting. Available data do not prove that chemotherapy plus radiotherapy yields superior survival compared with chemotherapy alone, although a reduction in local recurrence rate might be an important benefit. Before adopting preoperative short intensive radiation as a standard, the Swedish results should be confirmed, especially with more optimal surgery. Hence, the Dutch trial comparing total mesorectal excision (TME) plus or minus high fractional doses of preoperative radiotherapy is of considerable interest. This trial has completed accrual, results are awaited. The next trial (PROCTOR: preoperative radiotherapy and/or adjuvant chemotherapy combined with TME surgery in operable rectal cancer) will investigate the additional role of postoperative chemotherapy with 5-FU/LV after TME surgery whether or not preceded by short term irradiation.

Conclusions

The adjuvant treatment of colorectal cancer is indeed a promising field of research, with realistic hope for further improvement in the near future. Because the magnitude of the effects may be small, but relevant, the only way to progress further is with large-scale trials conducted on an international basis. In the US, the Intergroup and NSABP studies have shown that large-scale cooperative trials can be conducted within reasonable time. The PETACC adjuvant studies may serve as a model for such large-scale trials in Europe.

Controversial as the decision for premature closure of PETACC-1 may be [51] and regardless of the issues encountered in the process that has led to an early termination of this trial, for many other aspects this study has been successful. Recruitment has exceeded expectations and confidence remains that the PETACC intergroup structure is an appropriate way forward for conducting clinical trials in the field of adjuvant treatment of colorectal cancer.

Now that many different options for further studies have become available, there will be a strong competition among different companies to launch trials and to recruit patients. In fact, some trials have already been initiated that are run completely by the pharmaceutical companies. It is incumbent that we reflect carefully on how to improve the way of interacting with the pharmaceutical industry for future trials, particularly on how to preserve independent research and enforce strict clinical trial methodology and procedures.

It might be envisaged that the incorporation of new agents with different mechanisms of action in the adjuvant regimens may lead to a potentially meaningful impact on further advances in the treatment outcome and may open the way to individually tailored therapies.

References


37. Douillard JY, Cunningham D, Roth AD, et al. A randomized phase III trial comparing irinotecan (IRI) + 5FU/folinic acid (FA) to the same schedule of FU/FA in patients (pts) with