Adjuvant treatment of colorectal cancer.

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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. Adjuvant treatment of colorectal cancer is now widely accepted and can reduce mortality by approximately 10%. This can be considered as one of the major achievements in oncology from the past decade. Current results will be discussed and strategies for the future will be outlined, including ongoing or planned large-scale trials with new drugs and approaches.

Key words: chemotherapy, radiotherapy, colorectal carcinoma

ADJUVANT TREATMENT OF COLON CANCER

In 1988 and 1989, two large Cooperative Group trials showed a significant benefit for adjuvant chemotherapy in colon cancer. Opinion on the usefulness of adjuvant chemotherapy changed definitively when the results of the Intergroup study from the USA became available, although conflicting views were taken by European oncologists whose initial response was more conservative. 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. The evidence that adjuvant therapy is effective in colon cancer was further confirmed by different trials conducted in the US as well as in Europe. 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. Results from two large-scale USA studies (Intergroup 0089 and NSABP C-04) and the QUASAR trial from UK provided additional evidence that 5-FU plus LV in a weekly or monthly schedule for 6 months is currently the most widely accepted standard treatment in stage III colon cancer. There is no longer a role for the use of levamisole with 5-FU. In stage II colon cancer, adjuvant treatment is controversial and not generally accepted. Available data do not show a clear benefit and further research is needed.

Portal-vein infusion (PVI) of cytotoxic drugs is another method of adjuvant treatment that was popularized at the University of Liverpool, UK. However, results of different randomized studies that attempted to confirm the initial positive data were inconsistent. Two large studies, one from the EORTC and one from the UK (Adjuvant X-ray and Infusion Study) did not show a benefit from intraperitoneal infusion versus observation.

NEW TRIALS

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. In the 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 rapidly. In the first two trials standard bolus 5-FU plus LV (Mayo schedule) is compared with raltitrexed (Tomudex) (PETACC-1) or high-dose infusional 5-FU (PETACC-2). After randomization of 1835 patients within 15 months, unfortunately, PETACC-1 was closed to further randomization by the sponsor Astra-Zeneca before the target accrual of 2800 patients, due to an excess (1.8%) of drug-related fatalities in the Tomudex arm. As a result the analysis of this trial is postponed to 2003. 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/LV)
Table 1

<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>
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<tr>
<td>PETACC-2</td>
<td>Bolus FU/LV</td>
<td>Infusional FU+/- LV</td>
<td>Ongoing</td>
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<td>PETACC-3</td>
<td>Infusiona FU/LV</td>
<td>Inf FU/LV+CPT-11</td>
<td>Completed</td>
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<tr>
<td>PETACC-4</td>
<td>Surgery</td>
<td>Inf FU/LV+CPT-11</td>
<td>To be launched</td>
</tr>
<tr>
<td>PETACC-5</td>
<td>Chemotherapy</td>
<td>Chemoth followed by Celebrex</td>
<td>To be launched</td>
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<tr>
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<td>Infusional FU/LV</td>
<td>Inf FU/LV+Oxalipl</td>
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<td>Capecitabine</td>
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<tr>
<td>QUASAR-2</td>
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<td>Capecitabine+CPT-11</td>
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<td>Glaxo/Wellcome</td>
<td>Bolus FU/LV</td>
<td>Bolus FU/LV+Panorex</td>
<td>Completed*</td>
</tr>
</tbody>
</table>

*No benefit of Panorex

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 and capecitabine. The NSABP has closed a trial (C-06) that compared UFT/LV with FU/LV and results are awaited. A company conducted trial (X-ACT) in which capecitabine is compared with bolus 5-FU/LV has completed accrual. Enyluracil will not be developed further because of inferior activity compared to 5-FU/LV in advanced disease.

Additionally, irinotecan and oxaliplatin have different mechanisms of action compared to 5-FU and established activity in combination with 5-FU/LV in advanced disease. These drugs are now assessed in the adjuvant setting in the USA and Europe in combination with FU/LV versus FU/LV alone. In Europe PETACC-3 compared infusional 5-FU/LV with infusional 5-FU/LV plus irinotecan while bolus 5-FU/LV was utilized in the US trial (CALGB 89803). Another trial, conducted by Sanofi-Synthelabo, compared biweekly infusional FU/LV with the same regimen plus oxaliplatin (MOSAIC trial). In the USA the NSABP conducts a trial (C-07) assessing the addition of oxaliplatin to bolus 5-FU/LV. New projects include assessment of infusional FU/LV plus CPT-11 versus control in properly staged DukesB (PETACC-4) and chemotherapy followed by Cox-2 inhibition or placebo for 3 years (PETACC-5).

In Table 1 a summary of relevant trials is shown.

ADJUVANT TREATMENT OF RECTAL CANCER

Locoregional failure is clinically more important in patients with rectal cancer than in patients with colon cancer. Distant metastases are also seen in approximately 25% of patients. The aims of (neo-) adjuvant therapy before or after resection of rectal cancer are to improve local tumor control, to decrease distant metastases and to improve survival. Postoperative radiotherapy alone decreases slightly the local relapse rate but does not improve the survival. It is generally also accepted that postoperative chemotherapy alone does not increase survival although one trial did show a survival difference. Two American and a Norwegian study have shown that a combined modality approach with chemoradiotherapy after surgery provides a significant benefit in local and distant recurrences and an increased survival compared with either surgery alone, postoperative chemotherapy or postoperative radiotherapy. The picture is however not entirely clear and the superiority of postoperative radiochemotherapy over either modality alone has been questioned. In another trial continuously administered 5-FU during radiotherapy demonstrated a further significant effect on distant metastases and survival in comparison to a 5-FU concurrent bolus scheme. The main advantage of postoperative treatment is the optimal selection of patients based on surgical observations and pathologic specimen analysis. Europeans have generally turned towards preop-
ective radiotherapy. North American investigators are also evaluating more recently preoperative radiotherapy. Several types of radiotherapy regimens are used in the preoperative setting including: short-regimen of radiotherapy (5 x 5 Gy), surgery being planned immediately after radiotherapy, and a conventional long-course radiation (1.8-2 Gy/fraction: total 45-50.4 Gy), surgery being planned after a 4-6 weeks interval. The potential advantages of a preoperative approach over a postoperative one are: a decreased tumor seeding during operation, less acute and late toxicity, increased efficacy of radiotherapy and for patients who receive a conventional long-course of radiotherapy an increased rate of sphincter preservation. It is accepted that long-course radiation regimens can down-size a rectal cancer, whereas short-course radiation regimens do not induce down-sizing of the tumor. The long-course radiation regimens might therefore be more suitable for locally more advanced cancers. Several large randomized trials have tested preoperative radiotherapy in comparison to surgery alone and have demonstrated a lower local recurrence rate but no improved survival in most of the trials with preoperative radiation alone. The Swedish trial however, has shown to give an advantage in overall survival as well as in locoregional recurrence with the short-course preoperative radiation regimens (5x5 Gy). The Dutch Colorectal Cancer Group has shown that the addition of a short course radiation to optimal surgery (total mesorectal excision) still reduces the risk of local recurrence in all stages of rectal cancer: 2.4% versus 8.1% in the surgery alone group (p < 0.001), but did not improve the 2-year survival. Two randomized trials (NSABP R-03 and a German study) are testing preoperative versus postoperative conventional long-course radiation plus chemotherapy and the final results are pending. Data presented in abstract form from the NSABP study appear to favor the preoperative approach.

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. 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