Progress in the management of chemorefractory colorectal cancer

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1. Introduction

A multidisciplinary approach, combining advances in systemic chemotherapy, targeted agents and aided by better surgical and imaging techniques has significantly enhanced the outcome for patients with metastatic colorectal cancer (mCRC) over the last two decades (Fig. 1).\(^1\) Advancements in the management of unresectable mCRC have been characterised by small incremental improvements in overall survival which now extends beyond 2 years with the addition of biological agents to standard fluoropyrimidine-based chemotherapy regimens. Today, a whole host of newly identified targeted therapeutic agents inhibiting one or more key pathways are being evaluated in phase III clinical trials (including aflibercept and regorafenib)\(^2,3\) as potential new treatments for mCRC.

Our understanding of the benefits of targeted agents has been aided by large well-designed multicentre studies in patients with proven chemorefractory mCRC. While cetuximab initially showed only modest benefits in overall survival in unselected patients (Hazard ratio [HR], 0.77, 95% CI: 0.64–0.92),\(^4\) a subsequent study of patients with wild-type K-ras tumours revealed that cetuximab plus best supportive care (BSC) was associated with a doubling overall survival (median, 9.5 vs. 4.8 months for BSC alone; HR for death, 0.55; \(P<0.001\)) in chemorefractory disease.\(^5\) In the same way, the recent evaluation of regorafenib plus BSC showed only a modest improvement in overall survival (median, 6.4 vs. 5.0 months for placebo plus BSC; HR, 0.77 [95% CI: 0.63–0.94; 1-sided \(P=0.0051\)]) in patients with mCRC who progressed after standard therapies,\(^3\) but there is early evidence to suggest that some patients do benefit more than others.\(^3\) Like locoregional treatments, the challenge with targeted agents is to select the cohorts of patients who will benefit most. For targeted agents such as regorafenib, the decision to treat is likely to be based on the identification of a combination of molecular biomarkers (angiogenic signatures) for regorafenib activity.

2. Locoregional treatment with SIRT

The published evidence suggests that locoregional treatments may play a complementary role to systemic
treatment by improving the local control of metastases in the liver. Comparisons between these two treatment modalities cannot be made because the locoregional treatments are used to manage liver-limited or liver-predominant disease while clinical trials of systemic agents include a much broader group of patients including those with disease that has progressed beyond the liver to the lungs and peritoneum.

Early evidence for selective internal radiation therapy (SIRT) in mCRC was largely based on small case series. In review of the evidence in 2009, the Cochrane group concluded that there was a need for well-designed, adequately powered phase III trials to assess the effect of SIRT combined with modern chemotherapy regimens.6 Further studies with SIRT were also needed in chemorefractory disease, with a particular focus on the impact on quality of life.6 Since this review, four comparative or prospective studies have been published on SIRT in chemorefractory patients (Table 1).7−10 One such study at the University Hospitals Leuven in collaboration with other Belgian sites evaluated 44 patients with liver-limited mCRC for whom all other evidence-based treatments had failed.7 Patients were randomised to receive either protracted IV infusion of 5-FU (300 mg/m² day 1−14 every 3 weeks) or SIRT using 90Y resin microspheres plus 5-FU (225 mg/m² [cycle 1] then 300 mg/m² day 1−14 every 3 weeks, thereafter) until documented hepatic progression. Most patients had a good performance status (ECOG 0 or 1). The burden of liver metastases was similar in both treatment arms. The study found that median time to liver progression was significantly prolonged with the addition of SIRT compared to 5-FU alone (5.5 vs. 2.1 months; hazard ratio [HR] 0.38; p=0.003). The median time to progression at any site was also increased in the SIRT arm (4.5 vs. 2.1 months; HR 0.51; p=0.03), as was the disease control rate (86% vs. 35%; p=0.001). After 10 of 23 patients on 5-FU monotherapy crossed over to receive SIRT following progression, median overall survival was 7.3 and 10.0 months in the 5-FU and SIRT plus 5-FU arms, respectively (HR=0.92 95% CI 0.47−1.78; p=0.80). Grade 3 or 4 toxicities were recorded in 6 patients following 5-FU monotherapy and in 1 patient following SIRT plus 5-FU treatment (p=0.10). Adverse events associated with SIRT are generally mild and transient, including nausea, fever and abdominal pain (Table 2).
Table 2 – Adverse events profile with SIRT using 90Y resin microspheres in chemorefractory colorectal cancer liver metastases

<table>
<thead>
<tr>
<th>AE</th>
<th>Incidence</th>
<th>Characteristics</th>
<th>Prevention/Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>&gt;50%</td>
<td>Mild (grade 1*) onset on day of treatment for up to 1 week</td>
<td>None normally required</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>~50% (−10% grade 3−4)</td>
<td>Acute onset during treatment; self-limiting (normally &lt;24h)</td>
<td>May require narcotic (&gt;oral analgesia)</td>
</tr>
<tr>
<td>Nausea</td>
<td>~40% (&lt;5% grade 3–4)</td>
<td>Highest in treatment-experienced; self-limiting (normally &lt;24h)</td>
<td>Prophylactic anti-emetics</td>
</tr>
<tr>
<td>Fatigue</td>
<td>~40% (&lt;5% grade 3–4)</td>
<td>Onset in 1st month post-SIRT, normally subsides within 2 weeks</td>
<td>Adequate nutrition and hydration; prophylactic oral steroids</td>
</tr>
<tr>
<td>Abnormal Liver Function Tests</td>
<td>~20–40% (1–6% grade 3–4)</td>
<td>Particularly in combination with chemotherapy; transient: resolves in days (ALT, AST), weeks (bilirubin) or months (albumin)</td>
<td>None normally required</td>
</tr>
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More rarely, radiation-associated gastrointestinal ulcers can occur and these are more difficult to treat. Patients should be carefully monitored with a low threshold of suspicion for evidence of gastrointestinal ulcer to ensure early and effective treatment, especially if subsequent treatment with antiangiogenics such as bevacizumab is being considered.

In summary, SIRT is likely to play an important complementary role to systemic therapies for the control of colorectal liver metastases. Ongoing randomised controlled clinical trials with conventional chemotherapies with or without SIRT (in the first-line setting and in chemorefractory disease) will further define the role of this treatment modality in the management of liver-dominant mCRC.

Conflict of interest statement

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REFERENCES