ANTI-TUMOUR TREATMENT

Integration of neoadjuvant and adjuvant chemotherapy in patients with resectable liver metastases from colorectal cancer

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SUMMARY

The liver is the primary metastatic site in patients with colorectal cancer, and the only hope for a cure or prolonged survival in patients with liver metastases is provided by surgical resection. Advances obtained in non-resectable metastatic disease using new chemotherapeutic agents raise important questions about the use of neoadjuvant and adjuvant chemotherapy in patients with resectable liver metastases. Two major randomized studies have yielded positive results. First, a combined intra-arterial plus systemic fluoropyrimidine-based chemotherapy regimen demonstrated a relapse-free survival benefit when compared to systemic 5-fluorouracil–leucovorin therapy alone. This approach is still restricted to specialized centres, however, due to technical limitations and locoregional toxicities. Secondly, an EORTC trial demonstrated the superiority of peri-operative FOLFOX-4 chemotherapy in comparison to surgery alone. Oxaliplatin and irinotecan can induce substantial liver damage, especially steatohepatitis and vascular lesions, but the impact of these lesions on postoperative morbidity and survival remains unclear. Ongoing and planned trials will assess the addition of anti-angiogenic and anti-epidermal growth factor receptor agents to chemotherapy regimens.

Introduction

The liver is the major metastatic site in patients with colorectal cancer (CRC). The survival benefit of complete resection of metastases is now well established, with five-year survival rates of 25–50% in the most recent studies. After resection, however, 50–75% of patients relapse within the first two years. The liver is the site of relapse in half of cases, but other sites (especially the lungs and peritoneum) can also be involved. Starting with the efficacy of adjuvant chemotherapy after resection of stage III primary colon carcinoma and the survival benefit yielded by palliative chemotherapy in unresectable metastatic disease, several trials have focused on the role of chemotherapy in patients with resectable liver metastases. The results are particularly confusing, and many variables interfere with the interpretation of these studies, especially the administration route (locoregional and/or systemic), chronology (adjuvant and/or neoadjuvant), and agents used (fluoropyrimidine with or without oxaliplatin or irinotecan). This paper will review the recent studies and ongoing trials.

Locoregional and/or systemic chemotherapy

Regional liver chemotherapy infusion is a logical approach since the liver represents the prominent site of relapse after resection of hepatic metastases. This approach allows the delivery of high doses of chemotherapy to potential micrometastases remaining in the liver, while sparing extra-hepatic organs. Hepatic arterial infusion (HAI) with chemotherapy may also spare normal liver tissue. The liver has a dual blood supply; hepatic metastases derive their blood supply mainly from the hepatic artery, while normal hepatic cells preferentially depend on the portal vein.

Early studies evaluated 5-fluorouracil (5-FU)- or fluorouridine (FUDR)-based regimens in patients with initially unresectable metastases limited to the liver. These studies suggested efficacy...
of HAI. Ten randomized trials have compared HAI with fluoropyrimidine-based chemotherapy to systemic chemotherapy or best supportive care in patients with unresectable metastases. A recent Cochrane meta-analysis of these trials indicated, for a total of 1277 patients, that HAI was associated with a higher response rate (42.9% vs. 18.4% for systemic chemotherapy), but without significant advantage in terms of survival (15.9 vs. 12.4 months). The two studies with the best supportive care arm demonstrated a survival advantage for HAI, but it is now clear that best supportive care alone penalizes chemotherapy-naive patients with metastatic CRC. HAI with 5-FU was superior to that best supportive care alone penalizes chemotherapy-naive arm demonstrated a survival advantage for HAI, but it is now clear that best supportive care alone penalizes chemotherapy-naive arm. Nevertheless, the systemic bolus 5-FU-leucovorin regimen is now considered to be suboptimal. Altogether, these data do not support the use of fluoropyrimidine-based HAI alone in patients with initially unresectable liver metastases. The fact that the advantage of HAI in terms of response rate does not translate into any significant survival benefit is intriguing? It may represent evidence against the use of the locoregional route, but we must mention that this relative discrepancy between response rate and survival has been also observed for the systemic use of fluoropyrimidines. A meta-analysis by Buyse et al. showed that, when an optimized systemic fluoropyrimidine schedule (for instance infusional 5-FU, association with leucovorin…) was associated with a 20% increase of response rate by comparison to a standard bolus alone 5-FU, the median survival was prolonged by only 2 months, which is consistent with data described above for HAI. Finally, the non-significant benefit on survival yielded by HAI may be not specific to the administration way, but rather a reflection of the chemotherapy class.

HAI with oxaliplatin or irinotecan-based chemotherapy also achieved encouraging results in patients with initially unresectable metastases, with secondary resection of metastases in approximately 15–20% of the patients, and may be superior to HAI with fluoropyrimidines. All of these results led to the assessment of regional chemotherapy after resection of liver metastases. Initial studies indicated encouraging results, with 5-year survival rates between 13% and 57%. Nevertheless, most of these studies were performed in small series of patients. Other limitations included differences in the chemotherapy administration route (intra-arterial vs. intra-portal) and differences in the chemotherapy regimens (5-FU, doxorubicin, epirubicin, mitomycin C). Additionally, a high rate of recurrences in extra-hepatic sites was observed, especially in the lungs. Phase II studies assessing adjuvant HAI have shown promising results, but these studies have also been performed in limited series of patients. The main study conducted by Lorenz et al. enrolled 226 patients who were randomized to surgery alone or to surgery followed by HAI with 5-FU plus leucovorin. The median survival was 34.5 months in the chemotherapy group and 40.8 months in the control group, but this difference was not statistically significant. A Cochrane meta-analysis has been performed on seven randomized trials including the former trial, for a total of 592 patients. This meta-analysis showed that adverse events related to HAI were common, including five therapy related deaths. If the intra-hepatic recurrences were more frequent in the control group, overall survival was not increased by HAI, and even favoured the control group, though not significantly. The lack of survival benefit may be in part related to the morbidity of HAI. Additionally, when these trials have been conducted, no second line therapy was available after failure of first-line fluoropyrimidine chemotherapy. It is so possible that patients in the control arm (the chemotherapy-naive patients) benefited more from a conventional systemic fluoropyrimidine after tumour relapse than patients who previously have received HAI chemotherapy.

Based on these results, regional chemotherapy alone cannot be considered in an adjuvant setting after resection of liver metastases from CRC, but it would be interesting to better evaluate locoregional schedules containing oxaliplatin or irinotecan.

Locoregional plus systemic chemotherapy

The combined approach of locoregional and systemic chemotherapy is justified by the rate of extra-hepatic relapses after intra-arterial chemotherapy alone and highly effective new systemic regimens. The feasibility and efficacy of this schedule were first assessed in patients with initially non-resectable liver metastases, with responses rates of approximately 60% and acceptable toxicity. The main prospective randomized study assessing combined intra-arterial plus systemic therapy was performed at the Memorial Sloan Kettering Cancer Center (Table 1). After surgery, patients were randomly assigned to receive six cycles of HAI with fluorouridine plus intravenous 5-FU, with or without leucovorin, or six weeks of similar systemic therapy alone. Interestingly, the number of liver metastases was not limited in this study; 27% of patients had four or more metastases, a cut-off value frequently used in other studies. Significant improvement in survival at two years and liver relapse-free survival were observed in the combined-therapy group, and this was subsequently confirmed in an update.44 When stratified using the Blumgart’s risk scoring system, patients with high risk (score 3–5) seemed to benefit more from combined-therapy.45

The Memorial Sloan Kettering trial was the first to demonstrate the usefulness of adjuvant chemotherapy after resection of liver metastases. Still, some limitations have reduced its impact in general practice. The study was monocentric, and the control arm was somewhat inconsistent. Combined-therapy was associated with significant toxicity (primarily diarrhea, neutropenia or mucositis).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Randomized trials evaluating HAI plus systemic chemotherapy.</th>
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<tbody>
<tr>
<td><strong>MSKCC</strong></td>
<td><strong>ECOG-SOG</strong></td>
</tr>
<tr>
<td><strong>Experimental arm</strong></td>
<td>HAI FUDR + bolus IV 5-FU ± leucovorin</td>
</tr>
<tr>
<td><strong>Control arm</strong></td>
<td>IV 5-FU ± leucovorin</td>
</tr>
<tr>
<td><strong>Nb patients</strong></td>
<td>156</td>
</tr>
<tr>
<td><strong>Median RFS</strong></td>
<td>31.3 vs. 17.2 months</td>
</tr>
<tr>
<td><strong>2-Year RFS</strong></td>
<td>57% vs. 42%</td>
</tr>
<tr>
<td><strong>2-Year liver RFS</strong></td>
<td>90% vs. 60%</td>
</tr>
<tr>
<td><strong>4-Year RFS</strong></td>
<td>–</td>
</tr>
<tr>
<td><strong>4-Year liver RFS</strong></td>
<td>–</td>
</tr>
<tr>
<td><strong>Median overall survival</strong></td>
<td>68.4 vs. 58.8 months (ns)</td>
</tr>
<tr>
<td><strong>2-Year overall survival</strong></td>
<td>86% vs. 72%</td>
</tr>
<tr>
<td><strong>4-Year overall survival</strong></td>
<td>–</td>
</tr>
<tr>
<td><strong>Specific complications of HAI</strong></td>
<td>16/74 (21.6%)</td>
</tr>
</tbody>
</table>

Note: FUDR = floxuridine; RFS = relapse-free survival; ns: not significant.
Systemic adverse events, as well as local complications of the HAI (e.g., biliary sclerosis, catheter infection or thrombosis), might explain why only 26% of the patients allocated to the combined-therapy arm received more than 50% of the planned floxuridine dose. Consequently, this combined approach may be difficult to manage in non-specialized centres.

In another randomized study, postoperative chemotherapy combining HAI with FUDR plus continuous IV infusion 5-FU was compared to surgery alone.\textsuperscript{46} Accrual difficulties were encountered, probably explained by concerns about the surgery alone arm. The 4-year recurrence-free rate was 25% for the control arm and 46% for the chemotherapy group. No advantage was observed for overall survival.

More recently, schedules including oxaliplatin and/or irinotecan have been implemented. Kemeny et al. evaluated postoperative HAI with floxuridine in combination with systemic oxaliplatin, 5-FU and leucovorin in a phase I study.\textsuperscript{57} The use of HAI in association with systemic chemotherapy seems to reduce the risk of relapse. Additional reports, however, have indicated significant toxicity related to HAI, especially in the form of biliary sclerosis.\textsuperscript{46} Given the availability of newer, active systemic agents and regimens, the value of HAI chemotherapy has to be questioned.

**Systemic chemotherapy alone**

Using postoperative systemic chemotherapy has revealed an interesting trend of improved survival and reduced recurrence rates in retrospective studies. In a series of 235 patients, adjuvant chemotherapy was given to 99 patients, with most treatments being based on 5-FU-leucovorin.\textsuperscript{49} The 5-year survival rate was 53% in these patients and 25% in patients who did not receive chemotherapy.

The usefulness of postoperative therapy by bolus 5-FU-leucovorin has been assessed in two randomized studies\textsuperscript{50,51} (Table 2). These studies compared 6 months of postoperative chemotherapy to surgery alone, but both studies were closed prematurely as a result of slow accrual. A non-significant trend toward improvement of relapse-free and overall survival was observed. Recently, a pooled analysis of these studies has been reported.\textsuperscript{52} Out of a total of 278 patients, the median relapse-free survival was 27.9 months in the chemotherapy arm and 18.8 months in the control arm. In the multivariate analysis, patients in the adjuvant chemotherapy group had a significantly reduced risk of relapse (HR: 1.39, \( p = 0.026 \)). The median overall survival was 62.2 months in the chemotherapy arm and 47.3 months in the control arm, but despite a strong trend, the difference was not statistically significant.

Based on the results of these studies, the place of safe regimens such as LV5FU2 should be questioned after resection of liver metastases. Still, for several years many oncologists have proposed oxaliplatin or irinotecan-based regimens. These drugs have improved the survival of patients with initially unresectable metastases, and in some cases, have subsequently allowed resections.\textsuperscript{53–57}

The role of these drugs in patients with resectable metastases had first been assessed in phase II trials with promising results.\textsuperscript{58,59} Recently, though, the results of a randomized phase III trial conducted by the EORTC group were reported (Table 2).\textsuperscript{60} This trial compared the administration of 12 peri-operative FOLFOX-4 courses (6 preoperative and 6 postoperative) to surgery alone (this important study probably represents the last to contain a surgery alone arm). The trial enrolled 364 patients, all of whom had up to four liver metastases. In the chemotherapy arm, 78% of the patients received all six scheduled preoperative courses, with an overall objective response rate of 43.9%. The resection rate was similar in both arms (83.5% vs. 83.0%). Postoperative complications were slightly higher in the chemotherapy group, but chemotherapy-related toxicity was generally modest. The primary endpoint was the 3-year progression-free survival, which was 7.2% higher in the chemotherapy arm in the intent-to-treat analysis, 8.1% better if only eligible patients were retained, and 9.2% better if only patients who underwent a liver resection were selected. The studied approach of preoperative chemotherapy followed by postoperative chemotherapy in patients with resectable liver metastases is now considered by most specialists to be a standard. The overall benefit in this study was modest, however, and the superiority of the FOLFOX-4 regimen was in the same range as that observed in the above-mentioned studies assessing adjuvant bolus 5-FU-leucovorin.\textsuperscript{50–52} Additionally, in the intent-to-treat analysis, the difference between the two arms was not statistically significant, probably as a result of a lack of power. This lack of power may be due to an insufficient number of patients, but also to the selection criteria. The fact that the number of metastases did not exceed four, explains that both arms comprised patients with a "relatively good" prognosis, and patients in whom the magnitude of the benefit yielded by chemotherapy may be limited. Still, a limited number of patients received the 12 planned cycles. The overall survival in this study has not yet been published. A comparison of FOLFOX-4 to a fluoropyrimidine infusion schedule, such as LV5FU2, remains an important issue in terms of safety and cost, but based on current knowledge, this kind of study would likely be difficult for oncologists to ethically perform.

The role of irinotecan was assessed after complete resection of liver metastases in the European CPT-GMA-301 randomized trial.\textsuperscript{61} This trial compared 12 courses of FOLFIRI to 12 courses of LV5FU2 and enrolled 321 patients. The median disease-free survival was 21.6 for LV5FU2 versus 24.7 months for FOLFIRI (ns). We cannot exclude that these negative results were related to a significant effect of the LV5FU2 regimen or to a lack of efficacy of irinotecan in the adjuvant setting as in stage II or III colon cancer.\textsuperscript{62–64}

**Neoadjuvant and/or adjuvant chemotherapy**

One important issue is that the above studies do not address the crucial question of when to begin chemotherapy; i.e., before or after surgical resection of metastases? The chronology of chemotherapy

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**Table 2**

<table>
<thead>
<tr>
<th>Treatment arms</th>
<th>Setting</th>
<th>Nb patients</th>
<th>Relapse-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCDC-ACHTH-AURC\textsuperscript{50}</td>
<td>Bolus 5-FU + leucovorin vs. surgery alone</td>
<td>Adjuvant</td>
<td>162</td>
<td>33% vs. 24% at 3 years (ns)</td>
</tr>
<tr>
<td>EORTC-NCIC-GIVO\textsuperscript{51}</td>
<td>5-FU + leucovorin vs. surgery alone</td>
<td>Adjuvant</td>
<td>129</td>
<td>45% vs. 35% at 4 years (ns)</td>
</tr>
<tr>
<td>EORTC\textsuperscript{50}</td>
<td>12 FOLFOX-4 vs. surgery alone</td>
<td>Peri-operative</td>
<td>364</td>
<td>36.2% vs. 28.1% at 3 years (ns)</td>
</tr>
<tr>
<td>CPT-GMA\textsuperscript{53}</td>
<td>12 FOLFIRI vs. 12 LV5FU2</td>
<td>Adjuvant</td>
<td>321</td>
<td>24.7 vs. 21.6 (ns)</td>
</tr>
<tr>
<td>GERCOR (MIROX)</td>
<td>12 FOLFIRI vs. 6 FOLFOX-7 + 6 FOLFIRI</td>
<td>Peri-operative or adjuvant</td>
<td>284</td>
<td>Trial ongoing</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Analysis in eligible patients.
in the various trials was imposed as follows: peri-operatively in the EORTC trial and postoperatively in the FFCD-ACHBTH-AURC, EORTC-NCIC-GIVIO, and CPT-GMA trials. The exclusively adjuvant design is simple, limits the risk of including patients with extra-hepatic metastases, and ensures that all of the enrolled patients have had complete macroscopic clearance of metastases. On the other hand, neoadjuvant chemotherapy may render resectable initially unresectable metastases. This strategy contributes to selecting patients most suitable for surgery and to avoiding resection of progressive tumours. Indeed, a study by Adam et al. clearly demonstrated that the prognosis of patients with progressive metastases under preoperative chemotherapy was similar to that of patients who had no surgical resection.65 The situation is in fact more complex in clinical practice; for many multidisciplinary teams, chemotherapy is proposed after surgery in the case of metachronous metastases and is begun before surgery in case of synchronous metastases.

The exclusively postoperative policy may have led to preferential accrual of patients with metachronous metastases, which are associated with a better prognosis. This bias may have contributed to the lack of power of some studies. The peri-operative strategy adopted in the EORTC trial may have also induced selection bias. For instance, patients who underwent immediate resection of synchronous metastases at the same time as primary tumour resection were not included, nor were patients who underwent immediate surgery for metachronous metastases. It is likely that a single strategy will not be appropriate for all patients. The chronology of chemotherapy remains a crucial issue and should be addressed in future trials.

We integrated the issue of chemotherapy timing into the design of the ongoing phase III “MIROX” study conducted by the GERCOR group. This study is comparing 12 courses of the FOLFIRINOX regimen to an experimental schedule composed of 6 courses of FOLFOX-7 (in which the dose of oxaliplatin reaches 130 mg/m²) followed by 6 courses of FOLFIRI. This schedule may reduce the risk of oxaliplatin-related sensory neuropathy and may increase efficacy, given that there is no cross-resistance between oxaliplatin and irinotecan. Ethical concerns about the use of irinotecan may result from the fact that three randomized trials have failed to demonstrate a benefit of the use of irinotecan after resection of a stage II or III colon cancer.62–64 Yet, we considered that there was no ethical limitation for several reasons. First, in the main study performed in the adjuvant setting (PETACC-3 trial), after adjustment for the imbalance in TNM status between the two arms, the difference in disease-free progression for patients with stage III disease in irinotecan-LV5FU2 arm was rendered statistically significant.66 Secondly, after resection of liver metastases, a tumoral relapse will occur in a great majority of the patients. Consequently, we can not use the same rules that those used in the adjuvant setting after resection of a primary colon cancer. The post-metastases resection chemotherapy is probably more a first-line palliative chemotherapy than an “adjuvant” chemotherapy. In first-line palliative setting, irinotecan is known to have the same efficacy level than oxaliplatin. Thirdly, the rationale of the MIROX study was in part to reduce the oxaliplatin-related-sensoryneuropathy, which appears now to represent an important limitation for the use of FOLFOX in an adjuvant setting. A significant part of the patients indeed keep this neuropathy several years after chemotherapy. Finally, in the MIROX study, we hypothesized that irinotecan administered after oxaliplatin could increase the antitumour efficacy by reducing the repair of oxaliplatin-induced DNA damage. We have previously conducted a phase II trial in second line treatment of patients with metastatic colorectal cancer.66 In that study, we alternatively administered 4 courses of FOLFOX6 and 4 courses of FOLFIRI until progression of limiting toxicity. The results were promising with a 46% response rate.

The MIROX strategy was previously assessed in a phase II trial in 47 patients with resectable liver metastases.67 In 25 patients, chemotherapy was delivered entirely after surgery, while 22 patients received peri-operative chemotherapy (six cycles before and six cycles after surgery). The results were encouraging, with a 2-year relapse-free survival rate of 47%. For patients in whom chemotherapy was started before surgery, the objective response rate was 77%. The design of the ongoing phase III MIROX study is original. Upon entry into the study, patients are stratified based on three parameters: chemotherapy started before vs. after surgery, surgical resection vs. radiofrequency ablation with or without surgical resection, and a Blumgart’s prognostic score of 0–1 vs. 2–3 vs. 4–5. The latter stratification allows the inclusion of patients regardless of their number of metastases, although it does take this number into account. Several studies have demonstrated that the survival benefit after resection of more than four metastases is the same as the benefit obtained in case with fewer than four metastases, making it illogical to limit the number of metastases in clinical trials.68 Four other factors compose the Blumgart’s score: the interval between the primary tumour and the occurrence of metastases, nodal involvement of the primary tumour, size of metastases (<5 cm), and preoperative plasma carcinoembryonic antigen level (<340 mg/L).69 This kind of stratification is also in accordance with the recent recommendations from an expert panel.69 A peri-operative FOLFOX is recommended in case of more than one poor prognostic factor, even if the metastases are considered technically resectable. Yet, as mentioned later in the present manuscript, in case of a solitary small metastasis (<3 cm), up-front surgery is recommended to avoid a complete response which will render a secondary surgery hazardous. In all cases, a postoperative chemotherapy is recommended.

On the whole, the MIROX trial, initiated in 2002, is clearly a reflection of clinical practice, without selection of a definite subgroup of patients. The trial is planned to include 284 patients, and to date (August 2009), 251 patients have been enrolled.

The MIROX study so assesses the sequential administration of oxaliplatin and irinotecan. An important question is the potent role of the triple combination 5-FU-oxaliplatin-irinotecan (FOLFOXIRI or FOLFIRINOX regimens). The main study compared FOLFIRI to FOLFIRINOX in patients with unresectable liver metastases.70 FOLFOXIRI regimen was associated with a higher response rate (60% vs. 34%). This secondarily allowed a complete resection of metastases in 15% of the patients vs. 6% for FOLFIRI. An up-date indicated important survival rates at 5 and 8 years in patients who underwent a resection of metastases (42% and 33%, respectively).71 More recently the randomized phase II METHEP trial has been conducted on patients with metastases confined to the liver but initially considered to be unresectable.72 Various induction chemotherapy regimens were evaluated: FOLFIRI, FOLFIRX, High dose-FOLFIRI, FOLFOX-7, and FOLFIRINOX. On intent-to-treat analysis, after 4 cycles of treatment, among 122 patients evaluated (about 30 per arm), the most promising regimens appeared to be FOLFIRINOX (57% response rate) and High dose-FOLFIRI (47% response rate). Secondary resection rates of metastases were also highest in the High dose-FOLFIRI and FOLFIRINOX arms (37% and 36%, respectively). The trial should proceed to phase III. Generally, the safety profile of FOLFIRINOX or FOLFIRXIRI is acceptable. Their use in neo-adjuvant or adjuvant setting in patients with initially resectable liver metastases may so be reasonably questioned. Yet, some limitations exist. First, in the neo-adjuvant setting, the magnitude of the tumour response is not the critical objective, since metastases were already considered resectable. Triple combination may expose to “excessive” response (especially a complete response) which may render the metastases no more detectable for a secondary surgery. In the postoperative setting, the main question is how many cycles of chemotherapy could be delivered? It seems very
hypothetical to deliver twelve cycles of the triple combination for safety reasons. It is possible that this combination may allow shortening the adjuvant chemotherapy duration, by delivering for instance 6 cycles, and this is a pertinent question for a randomized trial.

The relevance of chemotherapy-induced liver damage

Preoperative chemotherapy may induce chemotherapy associated steatohapatitis (CASH) or a sinusoidal dilatation, which may increase the risk of infection and mortality after resection of metastases.73–75 In a retrospective report on 406 patients who underwent hepatectomy for metastases, 248 received preoperative chemotherapy.76 Chemotherapy consisted of fluoropyrimidine-based regimens alone, irinotecan plus 5-FU, or oxaliplatin plus 5-FU. A systematic analysis of chemotherapy-related liver injury was performed by histological examination. There were 36 patients (8.9%) with steatosis, 34 (8.4%) with steatohepatitis, and 22 (5.4%) with sinusoidal dilatation. Oxaliplatin was significantly associated with sinusoidal dilatation, while irinotecan was more likely to cause steatohepatitis. Patients with steatohepatitis had an increased 90-day mortality rate (14.7% vs. 1.6%). A recent study by Pawlik et al. performed on 212 patients, confirmed that the type of hepatic injury was regimen-specific, but preoperative chemotherapy was not associated with an increase in postoperative morbidity or mortality.77 In a study by Fernandez et al. severe chemotherapy-related steatohepatitis was more frequent in obese patients and affected the possibility of performing large liver resections.78 The requirement for intraoperative blood transfusions was increased in cases with severe vascular-induced chemotherapy injury in the study by Aloia, and the risk of postoperative complications was higher in patients who received ≥12 preoperative chemotherapy courses.79 The influence of the number of preoperative chemotherapy courses was particularly analysed in a study by Karoui et al. performed on 214 patients.80 A strong correlation was found with the risk of postoperative complications: the risk was 19%, 45% and 61% in patients who received ≤5, 6–9, and ≥10 chemotherapy cycles, respectively. These results suggest using only short preoperative treatments (2–3 months), considering resection of metastases as soon as they become resectable, and not waiting for the best tumour response. This is sufficient to provide chemo sensitivity data, and in case of a tumoural response, it will be possible to use the same chemotherapy schedule again after surgery. Moreover, a complete response to chemotherapy may complicate the subsequent surgical resection.

What to do in case of complete response after chemotherapy?

Modern chemotherapy regimens including oxaliplatin and/or irinotecan are associated with an important objective response rate, especially in patients with metastases limited to one organ. If the response rate is about 40–60%, the rate of complete responses is generally comprised between 5% and 10%.81 Additionally, in a significant proportion of patients in whom is obtained a partial response, some of the metastases may be rendered undetectable on imaging. In all these cases, it may be subsequently difficult for the surgeon to detect and remove all the initial tumoral sites. A crucial question is to know if the metastases that disappeared on imaging are sterilized. In a recent study, a pathological analysis of metastatic sites on complete response after neoadjuvant chemotherapy showed that a microscopic tumoural proliferation remained in more than 80% of these sites.82 So a radiological complete response does not mean cure in the majority of the patients, and it is recommended, if possible, to remove all visible scars or known metastatic sites. This is a major problem for patients with liver metastases initially considered resectable. Based on the results of the EORTC trial, the standard is now to propose peri-operative chemotherapy by FOLFOX. Yet, in case of small metastases, the rate of complete regression of some or all of the metastases is high after administration of 6 FOLFOX cycles. It may be preferable to perform the first radiological evaluation after 2 or 3 cycles in cases of isolated small metastases (<3 cm), or even to avoid preoperative chemotherapy, specially in case of metachronous metastases. These patients should be referred to the surgeon by the medical oncologist before the radiological disappearance of metastases.

The next step: targeted therapies?

Targeted therapies have substantially improved the prognosis of patients with unresectable metastatic disease. The anti-angiogenesis agent bevacizumab, a monoclonal antibody directed against the soluble vascular endothelial growth factor (VEGF), significantly increased survival when used in first or second line therapy in association with irinotecan or oxaliplatin, 5-FU and leucovorin.83,84 Pooled analysis of First BEAT and NO16966 indicated that, in patients with initially unresectable metastases, the front-line combination of bevacizumab to XELOX allowed a secondary resection of metastases in 215/1914 (11.2%).85 In a phase II trial by the GONO group, the combination of bevacizumab to FOLFOXIRI yielded a 76% response rate and a secondary resection of metastases in 17% of the patients.86 On the other hand, bevacizumab seems to lose its efficacy used in heavily pre-treated patients.87 These results suggest a higher efficacy of bevacizumab when used at early stages. Furthermore, in first-line palliative therapy, the benefit in terms of overall survival reaches five months, although the response rate is increased by only 10%. This suggests that the survival benefit achieved by bevacizumab is not exclusively explained by its action on macrometastases, but also by its action on micrometastases and even earlier at the so-called angiogenic switch.88 This is an important issue in the rationale of evaluating bevacizumab in an adjuvant setting after resection of stage II or III colon cancer. Several trials are ongoing or planned in this setting. It is also logical to assess the neoadjuvant efficacy of bevacizumab in patients with resectable liver metastases. Several studies have demonstrated an important role of VEGF in tumour recurrences after liver resection,89 however, the best treatment sequence must be defined. Preoperative use of bevacizumab may be limited by the increased risk of bleeding/wound-healing complications. The optimal time interval between stopping bevacizumab and subsequent surgery has not been clearly determined. Based on the pharmacokinetics of bevacizumab, it is recommended to wait at least 6–8 weeks after the last dose before performing hepatic resection and to postpone initiating bevacizumab during the 28 days following surgery.90 By respecting these guidelines, the risk of post-metastasectomy complications seems to be significantly decreased.91 In another recent study, 56 patients received six preoperative chemotherapy courses (XELOX regimen) and bevacizumab.92 The sixth cycle did not include bevacizumab, resulting in an interval of 5 weeks between the last bevacizumab administration and surgery. No patients required peri-operative blood transfusions, and only one experienced wound healing complications. More recently, safety data were reported from a retrospective study in 81 patients who received neoadjuvant bevacizumab plus chemotherapy and 40 patients who received chemotherapy alone.93 The interval between bevacizumab discontinuation and surgery for metastases was 31–117 days, and the risk of postoperative complications was similar to that observed in the chemotherapy-alone group. The Southwest Oncology Group 0408 ongoing phase II trial is currently assessing neoadjuvant therapy by bevacizumab–capecitabine–oxaliplatin.94 Other anti-VEGF and
multi-targeted tyrosine kinase inhibitors are also promising agents that will probably be assessed in patients with resectable metastases. The role of PTK/ZK has been assessed in the CONFIRM-1 study in first-line therapy for patients with metastatic unresectable CRC. In this study, the combination PTK/ZK with FOLFOX-4 was compared to FOLFOX-4 alone, but no benefit was demonstrated in terms of response rate, progression-free survival or overall survival.\(^{100}\) Thalidomide is currently being assessed in a phase II trial, conducted by the National Cancer Institute, following resection of recurrent or metastatic CRC.

Cetuximab is a monoclonal antibody directed against EGFR. It was first used in patients with advanced CRC in combination with irinotecan and after failure under an irinotecan-based chemotherapy.\(^{101}\) An initial phase II study assessed the combination of cetuximab to FOLFOX in front-line treatment of patients with initially unresectable metastases, with impressive results in terms of response rate (79\%) and interesting secondary resection rate of metastases (23\%).\(^{97}\) Yet, in subsequent studies, efficacy results were more modest.\(^{98}\) The CRYSTAL study compared FOLFIRI to FOLFIRI plus cetuximab in first-line therapy for patients with metastatic CRC.\(^{99}\) In that study, cetuximab yielded a small but significant benefit in terms of response rate and progression-free survival. Interestingly, the rate of resection of secondary metastases was slightly higher in the FOLFIRI-cetuximab arm (4.3\% vs. 1.5\%). If the addition of cetuximab yields a 10\% increase in response rate, this benefit translates into only a 2–3\% increase in complete resections and probably less than a 1\% increase in cure. Later, it was shown that the benefit of cetuximab was limited to patients whose tumour was negative for KRAS mutations.\(^{100}\) Similar results were obtained in the OPUS study comparing FOLFOX to FOLFOX plus cetuximab.\(^{101}\) As a result, the addition of cetuximab to chemotherapy is now possible in first-line therapy, and this strategy may be of particular interest in patients with metastases limited to the liver, which may be rendered resectable in case of a significant response. The use of cetuximab in patients with initially resectable metastases was also assessed in the EORTC 40051 “BOS” (Biologics Oxaliplatin Surgery) study. The aim of this randomized phase II study was to evaluate a peri-operative therapy composed of FOLFOX plus cetuximab with or without bevacizumab. Patients could have up to ten liver metastases, with up to two pulmonary metastases. This study is at least temporarily stopped, however, due to concerns regarding the combination of bevacizumab and anti-EGFR monoclonal antibodies, resulting from disappointing results with the combination chemotherapy-bevacizumab-pantumumab used in first-line therapy in the PACCE study.\(^{102}\) A randomized phase III trial of peri-operative chemotherapy (oxaliplatin–fluoropyrimidine) with or without cetuximab is ongoing in the United Kingdom.

EGFR tyrosine kinase oral inhibitors (gefitinib, erlotinib, ABX-EGF) may also be of interest, but their safety profiles seem to be insufficient when associated with chemotherapy, with an especially high frequency of grade 3–4 neutropenia and diarrhoea.\(^{103,104}\) In particular, recent phase II studies in patients with metastatic CRC have indicated that adding gefitinib to FOLFOX or FOLFIRI does not improve efficacy.\(^{105–108}\)

Conclusion

Several available studies now suggest a benefit of integrating neoadjuvant or adjuvant chemotherapy in patients with resectable or resected liver metastases. Combined HAI plus systemic fluoropyrimidine-based adjuvant therapy was the first schedule to significantly increase relapse-free survival; however, technical limitations interfere with the use of this regimen in clinical practice. Based on the results of an EORTC trial, peri-operative systemic chemotherapy with FOLFOX-4 can be considered to be the current standard. Based on the recent recommendations from a panel expert, peri-operative FOLFOLX should be proposed in all patients with resectable metastases.\(^{109}\) The place of neoadjuvant chemotherapy seems particularly appropriate if at least 2 poor prognosis factors are present: more than one metastasis, larger tumour \(\geqslant 5 \text{ cm}\), synchronous metastases, nodal involvement of the primary, high CEA level. In case of isolated small metastasis \((\leqslant 3 \text{ cm})\) it is wise to avoid neoadjuvant chemotherapy, or to carefully monitor tumoral response if neoadjuvant chemotherapy is decided (for instance synchronous metastasis, lymph node-positive primary). In that case, a tumoral evaluation could be performed after 2 or 3 cycles, and the patient referred to the surgeon before the occurrence of a complete response.

For the near future, several questions remain unanswered, though. Is FOLFOLX superior to LV5FU2? Is it possible to shorten the chemotherapy duration by using intensive regimens such as FOLFIRINOX? Is there a place for targeted therapies? Moreover, it is now likely that future trials will be carried out on selected subgroups of patients, in order to better reflect general clinical practice.

Conflict of interest statement

All authors disclose any financial and personal relationship with other people or organisations that could inappropriately influence (bias) their work.

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