Neoadjuvant Treatment for Liver Metastases of Colorectal Cancer

a report by
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Liver metastasis presents in approximately 50% of colorectal cancer patients, of whom 30% will already have liver metastases upon primary tumour diagnosis.[1] Moreover, upon *post mortem*, liver metastasis is the primary site of cancer spread in one-third of colorectal cancer patients.[2] A five-year survival rate of 21–43% has been noted in resectable colorectal cancer after complete surgical resection.[3,4] However, the majority of patients with liver metastases present with unresectable disease due to tumour size, tumour location or limited liver reserve.

Traditionally, patients with unresectable colorectal cancer were treated with palliative chemotherapy and had little chance of long-term survival.[5,6] Recently, advances in chemotherapy have been able to downgrade unresectable colorectal cancer and, in some cases, lead to resectable disease that qualifies for surgery. Neo-adjuvant chemotherapy is also being studied for the treatment of resectable colorectal cancer to improve survival rates; however, results have not yet been formally proved. Neo-adjunctive therapy with targeted agents is also being evaluated for use in combination with chemotherapy.

Neoadjuvant Chemotherapy

Unresectable Metastases

The classic chemotherapy regimen of 5-fluorouracil (5-FU) in combination with leucovorin (LV, folinic acid) has traditionally provided palliative care for patients with unresectable colorectal cancer. In the last 10 years, the addition of more efficient agents – oxaliplatin and irinotecan – has allowed initially unresectable patients to become resectable.[6–8] Early French retrospective studies reported that neoadjuvant chemotherapy in the form of chronomodulated 5-FU, LV and oxaliplatin (FOLFOX) could downstage disease in patients with initially unresectable liver metastases, thus enabling resection to be performed.[6,7] In the study by Bismuth et al., tumours were downstaged and became resectable in 16% of patients.[7] In a larger, updated study involving 1,104 patients considered to have initially unresectable colorectal liver metastases, 138 (12.5%) became resectable following chemotherapy. The majority of these patients (70%) were treated with a FOLFOX regimen.[9] In the resected patients, five- and 10-year survival was 33 and 22%, respectively. However, at median follow-up of 48.7 months, 80% of the resected patients had a tumour recurrence, of which 71% were in the liver. This high recurrence rate reflects both the severity of the initial metastatic disease and possible residual tumours.

The study also found four pre-operative factors associated with shorter survival times: rectal primary, three or more metastases, tumour size >10cm and carbohydrate antigen (Ca 19-9) >100UI/l. These results demonstrate that surgery should be offered to initially unresectable patients whose metastases are downstaged sufficiently by chemotherapy. Furthermore, the high tumour recurrence rate may reflect downstaging of the tumour by chemotherapy to such an extent that it could have apparently disappeared, whereas in reality active tumour persisted. For this reason, it may be prudent to refer patients to surgeons before obtaining a 'complete response', thus reducing the risk of surgery missing 'dormant' metastases.

A number of recent studies have evaluated neoadjuvant chemotherapy in primarily unresectable metastatic colorectal cancer.[10–18] The response rates in these studies vary between 6 and 37.5%, which could be due to differing classifications of unresectable disease. In the Mayo Clinic trial, 60% of patients had tumour reduction after neoadjuvant therapy with FOLFOX4 and 40% subsequently underwent successful surgical resection.[11] The use of 5-FU, LV and irinotecan (FOLFIRI) resulted in a 55% response rate in patients with colorectal cancer and liver metastases.[19] In this study, four patients underwent liver resection and all survived the follow-up period of 33 months. The authors concluded that the chemotherapy regimen was successful at downgrading unresectable disease with limited toxicity.

The combination of 5-FU, LV, oxaliplatin and irinotecan has been used to improve response rates to neoadjuvant chemotherapy. One randomised study evaluated response rates of oxaliplatin, irinotecan, LV and 5-FU versus FOLFIRI in unresectable chemotherapy-naïve patients with liver metastases only.[20] Resection was possible in 36% of patients in the oxaliplatin-containing arm compared with 12% of patients on the FOLFIRI regimen. Further long-term studies are required to directly compare survival and resection rates between the different chemotherapy combinations.

Another important question that remains to be answered is the optimal duration of chemotherapy before surgery. There is accumulating evidence that neoadjuvant chemotherapy, and in particular 5-FU, irinotecan and oxaliplatin, is associated with a risk of hepatotoxicity.[21–27] Thus, it could be argued that in patients with initially unresectable liver metastases, surgery should be performed as soon as the metastases become resectable, since delaying surgery and continuing chemotherapy may result in increased liver toxicity.

Resectable Metastases

The use of neoadjuvant chemotherapy in resectable colorectal cancer with liver metastases is currently under debate. It is argued that chemotherapy in patients with resectable disease could eradicate any undetectable metastases at the time of diagnosis and prevent further progression.

The final results of the European Organisation for the Research and Treatment of Cancer (EORTC) Intergroup randomised phase III 40983 study on peri-operative FOLFOX chemotherapy for patients with potentially resectable colorectal cancer liver metastases (CRLM) were reported in 2007.[28] A total of 364 patients with up to four CRLM were randomised to either peri-operative FOLFOX4 (oxaliplatin 85mg/m^2 and LV5-FU2) with six cycles before and six cycles after surgery (CT) or surgery alone (S). Eleven of 182 patients were ineligible in each arm, mostly due to more advanced disease, and 31 and 30 patients in the CT and S arms, respectively, could not undergo resection. At a median follow-up of 3.9 years, progression-free survival (PFS) was significantly better in the CT group (42.4 and 33.2% of resected patients in the CT and S groups, respectively).

Response to pre-operative chemotherapy has also been suggested as a means of predicting the success rate of surgical resection. In 131 patients who underwent liver resection for multiple CRLM, the influence of response to neoadjuvant chemotherapy on the outcome of surgical resection was evaluated.[29] Patients were divided into three groups after chemotherapy: group 1 had an objective response, group 2 were stabilised and group 3 had tumour progression. Disease-free survival (DFS) was 37, 30 and 8% for groups 1, 2 and 3, respectively, demonstrating an association between chemotherapy and surgical success rates. In contrast to this, Allen et al. noted no difference in survival rates between those who remained progression-free after neoadjuvant chemotherapy and those who did not receive pre-operative chemotherapy.[30]

As discussed earlier, systemic chemotherapy is associated with an increased risk of hepatotoxicity. As studies have yet to confirm that neoadjuvant therapy in resectable patients is beneficial, it is advised that the first-line treatment be surgical resection followed by chemotherapy in order to avoid unnecessary toxicity.

Neoadjuvant Targeted Therapies

Significant improvements have been made to the chemotherapy regimens used in metastatic colorectal cancer. However, there are still limitations. Targeted agents are now being investigated for use in combination with chemotherapy and as single agents to increase the efficacy of treatment. Three biologics are currently approved in Europe: bevacizumab (Avastin, Roche), cetuximab (Erbitux, Merck KgaA) and panitumumab (Vectibix, Amgen, Inc). Both cetuximab and bevacizumab have been studied for first-line treatment in colorectal cancer with liver metastases.

Bevacizumab

Bevacizumab is a monoclonal antibody (mAb) that targets the vascular endothelial growth factor (VEGF) and has shown little toxicity in phase I trials.[31] Bevacizumab has been shown to improve survival time and response rate both as monotherapy and in combination with standard chemotherapy regimens in patients with metastatic colorectal cancer.[32–34]

The pivotal trial for bevacizumab included more than 900 participants who were randomised to receive irinotecan with or without bevacizumab.[35] The addition of bevacizumab to irinotecan led to an increase in overall survival (OS) of five months and an improvement in PFS of four months compared with irinotecan alone. However, 11% of patients on the irinotecan–bevacizumab regimen suffered from

hypertension in comparison with just 2% in the irinotecan group, suggesting that bevacizumab should not be used in patients with a high risk of hypertension.

In the neoadjuvant setting, preliminary data from the First BEAT study, which included 1,965 patients with advanced colorectal cancer with primarily unresectable metastatic disease, found that 11.5% of patients were able to undergo surgery with curative intent following treatment with bevacizumab in combination with various standard chemotherapy regimens, including FOLFOX, FOLFIRI and capecitabine plus oxaliplatin (XELOX).[36] Of the evaluable patients, 704 had liver metastases, and in this population the overall rate for undergoing surgery with curative intent was 14.5%. It should be noted that this early data analysis reviewed safety and did not provide information on comparative efficacy between bevacizumab combination therapy and chemotherapy alone.

There has been concern that bevacizumab's anti-VEGF activity may have an impact on post-surgical wound healing, bleeding and liver regeneration.[37,38] This has led to recommendations that surgery be delayed for six to eight weeks following the last administration of bevacizumab,[39,40] although recent data in 39 patients with resectable tumours undergoing liver resection and/or synchronous bowel resection suggest that bevacizumab can be safely administered five weeks prior to surgery without increasing the rate of surgical or wound-healing complications or severity of bleeding.[41,42]

Cetuximab

Cetuximab is an immunoglobulin G1 (IgG1) monoclonal antibody targeted against epidermal growth factor receptor (EGFR). It has a clear indication in second- and third-line treatment of metastatic colorectal cancer and is currently being investigated both as monotherapy and in combination with chemotherapy in the first-line setting. A phase II trial of 300 patients compared patients receiving FOLFOX only with patients receiving FOLFOX–cetuximab.[43] A statistically significant difference in response rate was noted between patients with a performance status of 0–1: 49% for the cetuximab group compared with 36% in the FOLFOX alone group. Other phase II trials have also reported beneficial effects of cetuximab in combination with oxaliplatin-based chemotherapy.[44,45]

In safety and efficacy studies, cetuximab in combination with chemotherapy resulted in the downstaging of primarily unresectable tumours. In a phase II safety study, 23 patients were treated with cetuximab and FOLFIRI and seven became resectable.[46] The ACROBAT phase II study of FOLFOX4 plus cetuximab, conducted in 43 patients, showed a confirmed response rate of 72%. Ten patients underwent resection with curative intent of previously unresectable metastases.[47] The CRYSTAL phase III trial randomised 1,217 patients expressing EGFR tumours to receive FOLFIRI either alone or in combination with cetuximab.[48] The cetuximab group had a significantly longer PFS (the primary end-point) of 8.9 months compared with eight months in those treated with FOLFIRI only. Furthermore, an improvement in resection rates was noted in all patients – including, importantly, patients with liver metastases only. In the FOLFIRI–cetuximab group 9.8% could undergo surgical resection compared with 4.5% in the FOLFIRI alone arm. Long-term results in terms of OS rates and quality of life are still awaited in these patients.

Cetuximab is also being evaluated directly in the neoadjuvant setting. A phase II clinical trial evaluated the ability of cetuximab combined with FOLFIRI in downsizing initially unresectable metastatic colorectal cancer patients with liver metastases. Of the series of 23 patients, seven underwent resection of liver metastases.[49]

In a series of 151 patients with unresectable CRLM resistant to first-line chemotherapy, surgical resection became possible in 27 patients following addition of cetuximab to the chemotherapy regimen. Post-operative mortality was 3.7% and, after a median follow-up of 16 months, 92% patients who underwent resection were alive, with 40% disease-free. Median OS and PFS from initiation of cetuximab therapy were 20 and 13 months, respectively. Importantly, combination therapy with cetuximab in this series increased resectability rates without increasing operative mortality or liver injury.[50]

Cetuximab in Combination with Bevacizumab

Two pre-clinical trials have demonstrated a synergistic benefit of using both EGFR and VEGFR inhibition.[51,52] The BOND II trial evaluated the activity of combined targeted therapy in patients with advanced colorectal cancer, randomising 81 patients with advanced colorectal cancer to receive either cetuximab–bevacizumab–irinotecan or cetuximab–bevacizumab.[53] Response rates of 37 and 20% were reported for the irinotecan arm and targeted therapy arms, respectively. Median time to progression was 2.3 months longer in irinotecan-treated patients. A comparison between these results and those of the BOND trial, which contained similar patients, demonstrated that the addition of bevacizumab increased response and median time to progression.

The Cancer and Leukaemia Group B trial 80405 will test the value of combining cetuximab and bevacizumab in patients with metastatic colorectal cancer. Patients will be treated with chemotherapy and be randomised to receive a combination therapy with cetuximab–bevacizumab, cetuximab only or bevacizumab only.

Similarly, the EORTC has started a randomised BOS phase II trial that will enrol 100 patients with resectable metastatic colorectal cancer to receive either FOLFOX–cetuximab or FOLFOX–cetuximab–bevacizumab for three months as a first-line treatment. This will be followed by surgical resection and administration of the same treatment for another three months. The primary end-points will be safety and response to treatment. These trials will determine whether inhibition of both EGFR and VEGFR will be beneficial for the treatment of colorectal cancer with metastases.

Summary

Liver metastasis is present in approximately 50% of colorectal cancer patients and for the most part is unresectable. In patients with unresectable liver metastases the traditional standard of care was palliative; however, improvements in chemotherapy regimens, advances in surgical techniques – including portal vein embolisation, two-stage hepatectomy and local ablation – and the introduction of targeted therapies have greatly increased the options available. Neoadjuvant chemotherapy in patients with unresectable colorectal cancer has been demonstrated to downgrade metastases and, in some cases, allow for surgical resection with curative intent. Bevacizumab and cetuximab have both been shown to improve response rates and PFS if used in combination with neoadjuvant chemotherapy, and the addition of these targeted agents may result in higher resectability rates in a larger number of patients. The promise offered by neoadjuvant chemotherapy and targeted therapy means that collaboration between oncologists and surgeons is essential to optimise individual therapeutic strategies. ■

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