FEATURE ARTICLE

Metastatic colorectal cancer: are we talking about curability?

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Colorectal cancer (CRC) represents 10% of the total new cancer cases in the US and is the third-greatest cause of cancer mortality each year [1]. Patients die mainly from metastatic disease; however, the survival of those patients with metastatic colorectal cancer (mCRC) has improved dramatically over the last decade.

The median overall survival (OS), which was less than 6 months with best supportive care, reached 10–12 months with bolus 5-fluorouracil (5-FU) and up to 14 months with the addition of leucovorin (LV) in the bolus and infusional 5-FU/LV regimen. With the introduction of the sequential FOLFIRI/FOLFOX regimens, median OS reached up to 20 months [2].

During the last few years, better understanding of tumour biology has led to the development of biologic therapies that target two different mechanisms: angiogenesis (bevacizumab) and epidermal growth factor receptors (EGFRs) (cetuximab and panitumumab), with further improvement in the disease outcome.

However, there is an important question that should be asked: are we going towards curability in the setting of mCRC when surgery and chemotherapy are combined together? The combination of chemotherapy and surgery is currently accepted as the way forward to improve survival in patients with initially unresectable colorectal liver metastasis. The standard 5FU-based regimens together with irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) have been reported to facilitate the resection of 15–30% of initially unresectable metastases and with the initial integration of other novel agents, it is hoped that this can be further improved. However, this will require validation in large Phase III randomised clinical trials [3].

The definition of resectability has been changing over the past years, influenced in part both by the advances in surgical technique in the large specialised centres and the availability of a wide range of chemotherapeutic and targeted agents. The criteria for selection of patients should be based on multiple factors after multidisciplinary discussion. The team will be faced with three important questions or scenarios when assessing patients with mCRC: (i) patients with initially resectable metastatic disease; (ii) metastatic disease that is initially considered to be unresectable; and (iii) those who are unlikely ever to become resectable. In current practice and guidelines from different centres, surgery is offered to those with resectable disease, while palliative chemotherapy is offered to both those with initially unresectable disease and those with disease unlikely ever to become resectable. This should, however, raise other questions when we are dealing with such conditions: what is the clear definition of resectability; which combination of chemotherapy or chemotherapy plus targeted agents should be used; and do the hazards outweigh the benefits? These questions have been asked in various expert meetings but unfortunately no concrete answers have been found. In this review we will discuss these three questions.

Is the disease resectable or not?

This is a very important question that should be tackled during the multidisciplinary team discussions and the answer will depend on the experience of the team dealing with such conditions. It is clear that good 5-year survival rates can be obtained for patients with CRC liver metastasis by combining surgery and chemotherapy.

Historically, liver metastases were classified as unresectable if they were large in size, poorly located, multinodular or there was evidence of extrahepatic disease [4]. These classifications have not changed significantly and the criteria differ from one centre to another and from one country to another.

It is currently accepted that experienced surgeons can carry out all kinds of operations, including multiple resections, provided that there is sufficient remnant liver (>30%) and that the surgery is not too risky due to the location of the metastases (proximity to vessels in the anticipated remnant liver). Other considerations must include the presence of questionably resectable extrahepatic disease, poor tumour biology and age as they are not an absolute contraindication to surgery provided that the patient is fit and will be operated by an expert surgeon [5].

The general consensus of different panels is that there will never be a perfect definition for

resectability because of the different disease presentations. However, it is better to totally remove the metastatic disease than to leave it microscopically *in situ*, and R0 resection should be the target [3,5].

Unresectable disease: what is the best active regimen to be used?

Standard chemotherapy with 5-FU/LV-based regimens in combination with irinotecan or oxaliplatin can render initially unresectable metastases resectable and have also been shown to have an impact on OS. In addition, triple therapy combinations, for example FOLFOXIRI, or the addition of new targeted agents such as cetuximab or bevacizumab, are showing promising results with an increase in response rate (RR) but without solid impact on the OS [5].

Primary chemotherapy for patients with unresectable disease may allow at least 15–30% of patients to become candidates for optimal resection With this downsizing chemotherapy, OS has been greatly improved for patients who can benefit from this strategy. There is a clear relationship between RR to chemotherapy and the resection rate, and resectability should therefore be an endpoint for any strategy in mCRC, particularly given the fact that the more effective the chemotherapy, the better the chance for surgery. The combination of all these strategies can, however, only optimise resectability in up to 50% of patients with liver disease [6,7].

In patients with primary resectable disease, neoadjuvant and adjuvant chemotherapy approaches have been proven to be beneficial. With the recently published Eloxatin for Peri-Operative Use (EPOC) prospective randomised trial conducted by EORTC, which showed that 12 cycles of peri-operative FOLFOX4 used as neoadjuvant (six cycles) and adjuvant (six cycles) therapy increased the progression-free survival (PFS) of resected patients with a statistically significant benefit of 9.2% at 3 years in those patients who underwent resection [8]. The CRUK (Cancer Research UK) new EPOC study proposes to compare two treatment arms containing FOLFOX with or without cetuximab in neoadjuvant and adjuvant treatments [9].

Another important issue is the timing between chemotherapy and surgery, which is a key parameter for the optimal outcome for patients. The longer chemotherapy is administered and the higher the number of treatment lines, the lower is the survival after resection [10]. Moreover, looking for complete clinical response does not translate necessarily into complete pathological response and leads to the risk of tumour progression after the initial response [7]. In addition, it may become more difficult for the surgeon to detect lesions and may increase the risk of postoperative complications related to hepatotoxicity from prolonged chemotherapy. A complete radiological response should not be used as a primary endpoint if surgical resection is to follow, in order to prevent microscopic residual disease from being overlooked [11]. Determination of the optimal therapeutic window, which is as soon as the metastases become resectable, requires collaboration between the medical oncologist and the oncosurgeon.

In CRC, two main pathways have been successfully targeted. Bevacizumab targets and blocks vascular endothelial growth factor (VEGF) and inhibits angiogenesis, while cetuximab and panitumumab bind to the epidermal growth factor receptor (EGFR) preventing its activation.

VEGF inhibition

Two important trials have demonstrated that the addition of bevacizumab to chemotherapy in the first-line setting increases the activity without significantly worsening the safety profile of the cytotoxic drugs [12,13]. The addition of bevacizumab to irinotecan-based chemotherapy has shown promising efficacy with a median PFS up to 10 months and a median OS greater than 20 months. However, more recent data have shown less significant differences when bevacizumab was combined with oxaliplatin-based regimens [13]. Some data from this study indicated that in first-line therapy, bevacizumab should not be stopped before progression. Well-known biomarkers, such as *KRAS*, *BRAF* and *p*53 mutation status, do not influence the outcome of patients treated with a bevacizumab-based treatment.

EGFR inhibition

The human EGFR signalling pathway plays a key role in tumour growth and progression in numerous cancers. In CRC, EGFR signalling is deregulated. HER-1/EGFR overexpression correlates with disease progression, poor prognosis and reduced sensitivity to chemotherapy. Several agents target EGFR, including small-molecule tyrosine kinase inhibitors and monoclonal antibodies.

The standard chemotherapy regimens, FOLFOX or FOLFIRI, when combined with cetuximab, can result in >50% response rates in wild-type K-*Ras* tumours. Three main randomised clinical trials, CELIM, OPUS and CRYSTAL, have evaluated the resection rate of initially unresectable patients [14–16]. The CELIM study compared two treatment arms, both containing cetuximab, and combined with FOLFIRI or FOLFOX6 [16,17]. After eight cycles (4 months), in technically unresectable

disease, treatment was continued for four further cycles. In this study, the response rate reached almost 80%, allowing surgery in 43% of the patients, of whom 34% had R0 resection. In the CRYSTAL and OPUS studies, the addition of cetuximab to the cytotoxic backbone also led to an increased resection rate, although the number of resections remained low.

In the case of non-response to primary chemotherapy with either FOLFOX or FOLFIRI, the addition of cetuximab to second-line therapy can increase the number of patients whose cancers become resectable by about 50% [18].

Panitumumab use as a single agent when other therapeutic options have failed has so far been limited. However, it is a promising drug and its use should be validated in large Phase III randomised clinical trials.

Toxicity of treatment

Toxicity of the treatment should also be a main consideration in the choice of chemotherapy along with the number of total cycles to be given pre- and post-surgery. Patients will experience many of the usual side effects of chemotherapeutic agents (nausea, vomiting, myelosuppression and neuropathy); however, the lengthy duration of the chemotherapy cycles as well as the addition of targeted agents will lead to more severe side effects such as skin toxicity, hypertension and proteinuria. These side effects are manageable and treatment can be tailored to the patient without a major impact on the quality of life or to the surgical risk and should be a primary concern when dealing with patients with mCRC.

Future advances?

Most certainly, research and development for a better cure will not stop and there is always a 'new' in the field of cancer research. We are moving in to the era of tailored therapy when individuals will receive drugs based on their pathology as well as other considerations.

Valuable biomarkers will become one of these new considerations but only on the basis of scientific evidence. Their measure should be reproducible with high sensitivity and specificity and should have a clinically relevant impact on treatment. Certainly, *KRAS* testing has made a great impact on the disease natural history; and testing for multiple other indicators (PTEN loss, EGFR ligands, mutations in PI3K and *BRAF*, EGFR gene copy number and dual specificity phosphatases) may increase predictive power for resistance or response to treatment. However, these new predictive factors still await validation in clinical trials [19].

Another area of ongoing investigation is the mammalian target of rapamycin (mTOR). mTOR kinase has been identified as an anticancer target, and temsirolimus and everolimus have been approved in the treatment of renal cancer. These agents are being explored in colorectal cancer, although results have not yet been reported [20].

Conclusion

Not all patients should be treated the same; there is no particular standard treatment primarily in the up-front setting. The only standard option is whenever metastectomy is feasible it should be considered. Hope for a cure has to be the objective at the introduction of treatment in each patient.

Metastatic colorectal cancer is still an area under investigation and today's 'facts' may be obsolete tomorrow. Our patients need the best possible chance to stay alive and to have a chance for a cure; we need to use only validated data.

Multidisciplinary management of the patients from the onset of their disease is a prerequisite condition to offer them the best strategy and optimal timing for treatment.

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