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Potentially resectable metastatic colorectal cancer: An individualized approach to conversion therapy

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Contents

Abstract

Colorectal cancer is one of the most common cancers worldwide. In recent years, the survival of patients with metastatic disease has improved due to the developments in both medical and surgical care. Patients with technically unresectable metastatic disease could benefit from a multidisciplinary approach for their possible shift toward a technically resectable condition; the choice of the most effective systemic treatment is then crucial to allow conversion to resectability. Systemic conversion therapy may include chemotherapy agents' combinations (fluoropyrimidine, irinotecan and oxaliplatin), with or without targeted agents (cetuximab, panitumumab, bevacizumab). The choice of the best treatment option has to be evaluated by taking into account each patient's baseline characteristics, biological and pathological information and surgical strategy. In particular, the role of some biologic characteristics of the disease, namely the mutational status of EGFR-pathway oncogenes, is emerging as an important predictive factor of response to anti-EGFR targeted agents. Patients presenting with colorectal cancer metastases should be evaluated for multimodal management with curative intent as the appropriate chemotherapy regimen may induce tumor shrinkage, conversion to resectability and improved survival.

Keywords: Conversion therapy; Colorectal cancer; Colorectal cancer metastases; Metastasectomy; Targeted therapies; Chemotherapy; Resection

1. Background

Colorectal cancer (CRC) is one of the leading causes of death from cancer worldwide [1]. In recent decades, the survival of patients with metastatic CRC (mCRC), has

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dramatically improved due to the developments in both medical and surgical care [2]. In selected patients, surgery can be included in the treatment plan, as the resection of hepatic metastases improves progression-free survival (PFS) and may offer the chance for cure in approximately 10–25% of patients [2–8].

A thorough evaluation must be carried out to determine the appropriate treatment strategy for every patient diagnosed with mCRC. A first analysis should be made to distinguish between patients with oncologically non-resectable disease (such as those with multiple sites of metastatic disease), who will never be considered for surgery even after responding to medical therapy, from patients with technically unresectable metastases, who are regarded as "temporarily" unresectable, and must be carefully evaluated in the course of primary systemic treatment for their possible shift (conversion) toward a technically resectable condition. Indeed, at present the definition of resectability is solely technical and based on the possibility to completely resect all visible metastases leaving an adequately functioning parenchyma [9]. This definition of resectability, by excluding all tumor features, implies that each patient must have its disease managed by a multidisciplinary team, including medical oncologist, radiologist, interventional radiologist, and radiation therapist, where all the specialists involved can correctly define the resectability status [10] and reassess the surgical option in case of tumor response.

Regarding systemic therapy, medical treatment, administered in the case of primarily unresectable disease, which is capable of converting the disease to a resectable status, is generally referred to as "conversion therapy".

In this review we overview the possible therapeutic options for patients with initially unresectable mCRC, focusing on individualized approaches to conversion therapy in a multidisciplinary strategy.

2. Conversion therapy

Since the 1980s, chemotherapy for CRC has been based on fluoropyrimidine-5-fluorouracil (5-FU), alone or in combination with leucovorin (LV). Advances in clinical research have progressively led to the use of newer agents, namely irinotecan and oxaliplatin as chemotherapy drugs, and cetuximab, panitumumab, bevacizumab, aflibercept and regorafenib as targeted agents [11–14].

Most of the results in terms of efficacy and tumor shrinkage can be extrapolated from studies that used different chemotherapy regimens in the palliative setting. The majority of patients enrolled had an "oncologically unresectable" disease, being PFS or overall survival (OS) the primary endpoint. The metastasis resection and conversion rates were then evaluated retrospectively and no clear definition of resectability was provided. The efficacy of chemotherapeutic associations in doublets or triplets has been established [15–21] and afterwards, also the association between chemotherapy and monoclonal antibodies has proven to be effective [13,22–36]. The results in terms of OS and overall response rate (ORR) of the main phase II and III studies are summarized in Table 1.

Several studies have investigated the use of different schemes in the specific setting of conversion therapy; all these trials have explored the association of chemotherapy with monoclonal antibodies (MoAbs).

The phase II BOXER trial evaluated bevacizumab, a MoAb against VEGF, in association with a capecitabine and oxaliplatin (CAPOX) chemotherapy regimen in patients ineligible for upfront surgery, which resulted in an ORR of 78%. The conversion rate in this trial reached 40%, with 12 out of 30 patients judged to be resectable after treatment [35].

In the randomized phase II trial OLIVIA, bevacizumab was evaluated in association with mFOLFOX6 or FOLFOXIRI. The response rate (RR) was higher in the FOLFOXIRI-bevacizumab arm (80.5% vs. 61.5% in the FOLFOX arm; $p = 0.061$). Although this value did not reach statistical significance, radical (R0) resection rate was significantly higher in the FOLFOXIRI-bevacizumab arm (48.8% vs. 23.1%; $p = 0.017$) [27].

Other studies evaluated the use of anti-EGFR monoclonal antibodies in the conversion setting. As will be further discussed below, during the clinical development of these drugs (cetuximab particularly) the mutational status of KRAS was recognized as a predictive marker of response to therapy. As a result, in older studies, patients were unselected and the evaluation in the KRAS wild type (KRASwt) population was performed retrospectively.

The CELIM phase II randomized trial compared the association of cetuximab with FOLFIRI and FOLFOX6 in patients with non-resectable liver metastases. The difference between the two groups, in terms of RR, was not significant. Tumor response, evaluated in a retrospective analysis, was significantly higher in patients with KRASwt tumors (70% vs. 41%, $p = 0.008$). R0 resection was possible in 38% of patients in FOLFOX6-cetuximab arm and 30% of patients in FOLFIRI-cetuximab arm. According to the retrospective review, resectability rates increased from 32% at baseline to 60% after chemotherapy ($p < 0.0001$), regardless of the regimen used [37].

In a recent phase II randomized trial, patients with KRASwt synchronous non-resectable liver-limited metastases were assigned to receive chemotherapy alone (FOLFIRI or FOLFOX) or in combination with cetuximab. The ORR was 57.1% in the association arm and 29.4% in the chemotherapy only arm ($p = 0.001$), with a R0 resection rate of 25.7% and 7.4%, respectively ($p = 0.04$) [36].

The impact of panitumumab as a part of a conversion strategy has been investigated in the MetaPan phase II study, in which panitumumab was associated with a doublet chemotherapy containing capecitabine and oxaliplatin (XELOX). In patients with KRASwt tumors, the ORR was 60%, with a conversion rate of 42% of initially unresectable patients being able to undergo curative surgery [30].