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PRE-OPERATIVE CHEMOTHERAPY FOR COLORECTAL CANCER WITH LIVER METASTASES AND CONVERSION THERAPY

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Abstract: *Preoperative treatment of resectable liver metastases from colorectal cancer (CRC) is a matter of debate. More than 50% of patients with colorectal cancer develop liver metastases. Surgical resection is the only available treatment that improves survival in patients with colorectal liver metastases (CRLM). Neoadjuvant and conversion chemotherapy may lead to improved response rates in this population of patients and increase the proportion of patients eligible for surgical resection. The present review discusses the available data for chemotherapy in this setting.*

Keywords: *Colorectal cancer, Pre-operative chemotherapy, Liver metastases.*

INTRODUCTION

Colorectal cancer (CRC) is the third tumor incidence in the world with over 940,000 new cases and nearly 500,000 deaths annually worldwide[1]. About 50% of CRC patients has, diagnosis, distant metastases, and overall survival (OS) does not exceed two years[2,3]. The liver is involved in 80-90% of cases, and in almost half of patients at stage IV, is the only site of metastasis. The integration of chemotherapy and surgery in the treatment of liver metastases (LM) represents the more modern approach and is able to increase the survival in this subgroup of patients[4] with an approximately 10% of patients cured.

About a third of patients with CRC extensive LM resectable presents *ab initio*, and it recently acquired that surgery is the first therapeutic which must follow a systemic adjuvant chemotherapy[5].

The standard treatment of CRC patients with LM is systemic chemotherapy; however, despite recent advances, the 5-year survival is poor. About a third of patients with CRC with extensive liver disease presents *ab initio* resectable metastases, and it recently acquired that surgery is the first therapeutic which must follow a systemic adjuvant chemotherapy[5]. On the other hand, in patients who undergo immediate radical surgical resection of LM, the 5-year survival reaches 30-40%.

Retrospective studies show an advantage in terms of OS in patients who undergo hepatic resection with respect to patients treated only with chemotherapy[6,7], but it is commonly felt that the

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advantage evidenced with surgery is at least partially due to patient selection (better performance status and smaller disease extension in patients treated with surgery).

Patient selection for primary liver resection of CRC metastases

In most cases, the patients with LM are not eligible for radical surgical resection. Historically, the main contraindications for a surgical approach have been: > 4 metastases, presence of extra-hepatic disease and resection margins < 1 cm[8]. Bismuth et al[9] have extended these criteria allowing resection of more metastases and of multinodular or hilar metastases. A consensus group has proposed new guidelines for the evaluation of resectability of LM. Their unresectability criteria are: 1) hepatic disease that involves more than 50% of liver parenchyma or six segments, 2) extra-hepatic disease, 3) unfit patients[10]. However, consensus on the definition of resectability criteria varies considerably among centres. The patients candidated for radical hepatic resection can be stratified into risk groups on the basis of clinical scoring systems[11-13], which use prognostic factors identified with multivariate analysis, such as the presence of positive lymph nodes, a < 12 month disease-free survival, the presence of more than one tumour, high preoperative CEA, a > 5 cm tumour. According to the above factors, the 5-year survival has been shown to range between 14 and 60%. The validity of these guidelines needs to be confirmed in further trials before becoming a standard approach to patients with liver metastases from CRC.

Pre-operative chemotherapy

The importance of a possible preoperative therapy derives from the observation that, unfortunate, the majority of patients undergoing liver resection relapse after surgery. For this reason, new approaches have been investigated in recent years. A EORTC randomized controlled trial demonstrated a significant advantage in terms of progression-free survival (PFS) in patients treated with peri-operative chemotherapy[14].

Pre-operative chemotherapy could make resectable LM in patients with initially unresectable disease and could increase the percentage of radical resections. This approach allow limited hepatectomies in patients with initially resectable LM, with the aim of reducing surgery-related morbidity and improving post-operative recovery. Pre-operative chemotherapy could eradicate micrometastases, offering a test of in vivo chemosensitivity which could possibly be useful for the determination of an optimal post-operative medical approach.

Regarding the neoadjuvant chemotherapy, the optimal regimen has not yet been determined. However, as in the metastatic setting, the combination of chemotherapy with biological agents appears to offers the best results.

Nasti and others[15] investigated the feasibility and activity of bevacizumab plus FOLFIRI in this setting.

A single-stage, single-arm phase 2 study design was applied with 1-year progression-free rate as the primary end point, and 39 patients required. From October 2007 to December 2009, 39 patients aged 18-75 years, PS 0-1, with resectable liver-confined metastases from CRC received bevacizumab 5 mg/kg, followed by irinotecan 180 mg/m^2, leucovorin 200 mg/m^2, 5-fluorouracil 400 mg/m^2 bolus and 5-fluorouracil 2400 mg/m^2 46-h infusion, biweekly, for 7 cycles. Bevacizumab (Beva) was stopped at cycle 6. The objective response rate was 66.7% (95% exact CI: 49.8-80.9). Of these, 37 patients (94.9%) underwent surgery, with a R0 rate of 84.6%. Five patients had a pathological complete remission (14%). Out of 37 patients, 16 (43.2%) had at least one surgical complication (most frequently biloma). At 1 year of follow-up, 24 patients were alive and free from disease progression (61.6%, 95% CI: 44.6-76.6). Median PFS and OS were 14 (95% CI: 11-24) and 38 (95% CI: 28-NA) months, respectively. The authors concluded that the preoperative treatment of patients with resectable LM from CRC with Beva plus FOLFIRI is feasible, but further studies are needed to define its clinical relevance.

Retrospective analyses and data from phase III studies on metastatic disease showed that some patients initially treated with a palliative intent became susceptible to radical resection of their LM[17,18]. Tournigand et al[16] evidenced a 54% OR rate for the combination of 5-FU/FA and OXA (FOLFOX) and of 56% for the combination of 5-FU/FA and IRI (FOLFIRI). Liver metastases treated with FOLFOX resulted resectable in 13% of cases, while those treated with FOLFIRI were resectable in 7% of cases. Goldberg et al[17] compared FOLFOX with a combination regimen of IRI and bolus 5-FU/FA (IFL) and with the association of OXA and IRI (IROX), evidencing an OR rate significantly higher for the FOLFOX regimen (45% vs 31% vs 35%, respectively). In this study the percentage of patients who subsequently underwent surgery with radical intent after FOLFOX (4.1%) was also higher than after IFL

(0.75%)[18]. A phase III study published by the Gruppo Oncologico Nord Ovest (GONO) compared fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) with FOLFIRI as first-line chemotherapy in unresectable metastatic colorectal cancer. Response rates as assessed by an external panel was 34% (FOLFIRI) versus 60% (FOLFOXIRI) ($p < .0001$). Interestingly, the R0 resection rate of metastases in liver-limited disease was greater in the FOLFOXIRI arm (12% v 36%; $p = .017$). Progression-free survival and OS were both significantly improved in the FOLFOXIRI arm (median PFS, 6.9 v 9.8 months; hazard ratio [HR], 0.63; $p = .0006$; median OS, 16.7 v 22.6 months; HR, 0.70; $p = .032$)[19].

Adam et al reported an update of the aforesaid data with an analysis of 701 patients; radical resection was possible in 14% of patients with a 5-year survival of 35%[19]. Giacchetti et al analyzed 151 patients initially considered unresectable for the presence of large LM (> 5 cm), multiple metastases (> 4 nodules) or metastasis localized in the hepatic hilus. All patients were treated with an oxaliplatin-containing chemotherapy regimen. Objective response rate was 59%. After chemotherapy, 51% of patients were considered resectable but only 38% of patients underwent radical resection. The median survival was 48 months for the resected patients and 15.5 months for the unresected ones[20].

Alberts et al analyzed 42 patients treated with FOLFOX4 reporting a 62% OR rate, a 33% of hepatic resections and a median survival of 31.4 months in resected patients[21]. Quenet et al evaluated 34 patients treated with a chemotherapy regimen containing oxaliplatin, irinotecan and 5-FU, obtaining resection of hepatic disease in 37,5% of patients[22]. Pozzo et al treated 40 patients with FOLFIRI, obtaining an objective response in 47,5% of patients and resection of LM in 27.5% of patients. The median survival of resected patients had not yet been achieved after a median follow-up of 30.4 months[23]. Also, Benoist et al analyzed 38 patients derived from a prospective mono-institutional series of 586 consecutive patients treated for LM from CRC. The authors' objective was to perform liver resection, including the sites of the disappeared LM in patients with resectable metastases. In initially unresectable patients, resection or local ablation of all visible LM was performed, leaving the disappeared liver metastases in the remnant liver. Of the 38 patients, 22 had unresectable LM (multiple bilobar deposits in 20 patients and invasion of major liver vessels in 2 patients) while 16 patients had resectable disease. Complete radiological remission (cRR) was upholded by liver examination and US during surgery in 15 patients who had initially resectable disease. Anyway, pathologic examination of the cRR resected areas showed the presence of viable tumour cells in 12 patients (80%). Recurrence was observed 1 year after liver resection in 10 patients (66.6%). After 1 year, 14 of 15 patients were alive. In initially unresectable metastases liver examination and intraoperative US upholded that there were no remaining visible tumour at the site of 31 LM that had a cRR; these lesions were not resected. At 1 year, 23 patients (73%) developed recurrences at the site of the unresected lesions[24]. Benoist et al showed that although radiological complete response may be a useful criterion for evaluating the efficacy of chemotherapy, it does not mean a potential cure. Therefore, a systemic chemotherapy with neoadjuvant intent in patients with initially unresectable LM from CRC looks a potential therapeutic weapon. Anyway, which is the optimal neoadjuvant regimen and how many cycles are more appropriate before surgery it is still debated. Several issues remain open: the planned curative resection should be determined by radiogralogical response? Does the response to neoadjuvant chemotherapy condition the continuation of the same therapy after surgery? Therefore, all patients with initially unresectable LM from CRC should always be aimed by a multidisciplinary team to define the best treatment program.

Also, for the high perioperative morbidity rates, all patients with resectable LM eligible for neoadjuvant chemotherapy require accurate risk/benefit evaluation. Gruenberger et al[25] studied 50 patients with resectable LM (1 metastasis 30%; 2-3 metastasis 22%; > 4 metastases 48%) treated with a neoadjuvant regimen containing oxaliplatin (30 patients with XELOX, 20 patients with FOLFOX4). All patients underwent surgery and obtained hepatic resection R0, with no surgery-related deaths and a morbidity of 12%. At a preliminary follow-up, 58% of patients were disease-free, 20% had relapsed and 22% had died.

Besides, do not forget that there are two main types of liver damage have been reported: vascular changes and chemotherapy-associated steatohepatitis[26-29].

In conclusion, these data suggest the use of biologic agents in the neoadjuvant setting and open a real opportunity for pursuing curative resection also in patients with initially unresectable LM. Both cetuximab and and bevacizumab appear equally effective in combination with chemotherapy. The addition of cetuximab should be preferred in patients with wild-type KRAS tumors. Data from CRYSTAL and OPUS are pooled from subgroup analysis within large phase III studies in

the metastatic setting and thus, they suffer of statistical pitfalls. Prospective, ad hoc trials are warranted in the near future in order to assess the effective role of biologic agents in the neoadjuvant setting and establish which targeted agent is the preferred combination partner for specific chemotherapy.

Neoadjuvant chemotherapy and the introduction of biologic agents

At the present, the best choice in the management of patients with unresectable LM consists of pharmacological treatments characterized by high response rate for a limited number of cycles, and then instrumental re-evaluation of the disease to define again the susceptibility to curative surgery (the so-called "conversion chemotherapy") and, in the alternative, a systemic treatment to palliative purposes only.

The Conversion Therapy is given to patients in good overall clinical condition, with limited metastatic disease, mainly liver, for which a systemic drug treatment plays a decisive role. It could, in patients in quick response, allowing a potentially curative surgery on secondary injuries. Therefore, in this subpopulation of patients regimes characterized by high response rate are preferred, regardless of their ability to impact on survival.

The systemic treatment consist in a combination of two drugs (5-fluorouracil, and oxaliplatin or irinotecan) with a response rate that does not exceed 40%.

The randomized Phase II called "CELIM"[30] was designed to evaluate the effectiveness of adding Cetux to FOLFIRI or FOLFOX6 in the neoadjuvant treatment of patients with unresectable CRC LM (technically unresectable according to the evaluation of the radiologist and the surgeon, or number of metastases >5). Main objective of this trial was to evaluate the response rates and, among the secondary, the evaluation of patients brought to resection.

Patients were considered eligible in the presence of a massive hepatic involvement, assuming the possibility of surgery in case of good response to chemotherapy.

One-hundred-eleven patients were enrolled and randomized to receive FOLFOX6 plus Cetux (56 patients) or Cetux plus FOLFIRI (55 patients).

The analysis of the status of EGFR, KRAS and BRAF was conducted retrospectively. Patients were evaluated for resectability by the local surgical team after the first 16 weeks of therapy and then every 8 weeks to 2 years. A group of 7 between radiologists and surgeons has reviewed all the images independently, without knowing the details about the medical history of each patient (Figure 1).

The response rate was 68% in patients treated with Cetux plus FOLFOX 6 and 57% in those in the FOLFIRI arm, difference is not statistically significant. A retrospective analysis showed a higher rate of response in both arms in patients wild type, both as regards the only KRAS (70% versus 41% in the mutant, $p = 0.008$) that both genes KRAS and BRAF (72% versus 40%, $p = 0.003$). The percentage of subjects radically resected (RO) was 38% with Cetux and FOLFOX6 and 30% with Cetux plus FOLFIRI, with a significant increase in surgery patients compared to

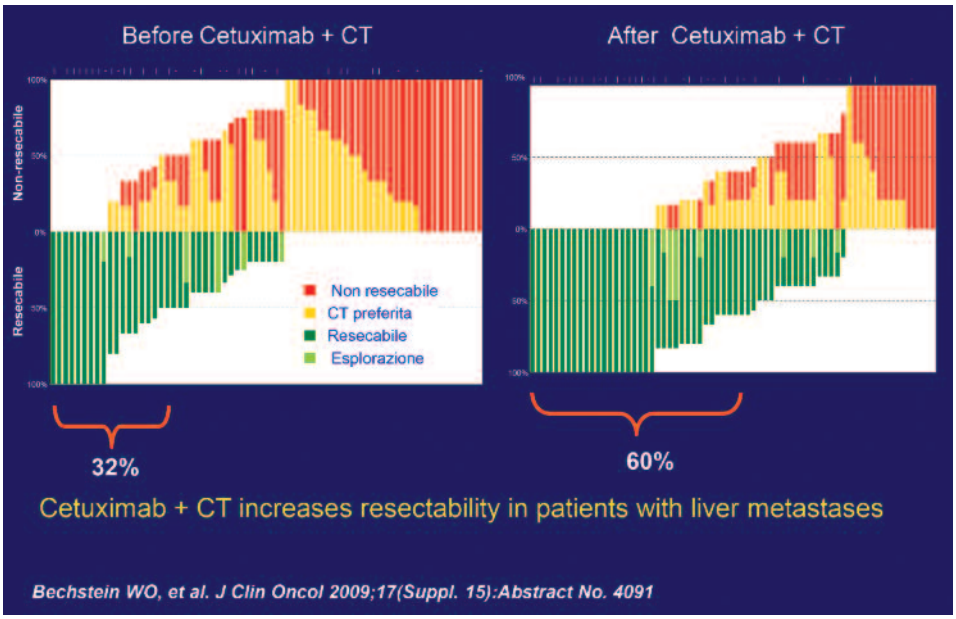

Figure 1. CELIM: resectability based on blinded assessment of seven surgeons.

baseline as further confirmed by an independent review committee in blind (= 28%, $p < 0.0001$).

The tolerability profile of the treatment, as well as the rate of perioperative morbidity, have not presented significant differences with respect to what has been reported in the literature.

The surgical approach in case of tumor progression for resectable CLM

The surgical approach in case of tumor progression for resectable CLM is largely debated in literature since a study from Adam R. et al who demonstrated a significant worst survival after LR of progressive CLM.

Despite that, a recent study from Vigano et al[31] reviewed a survey register of 6,025 patients underwent complete liver resection (R0/R1) between 1998 and 2009.

They founded that early recurrence risk is enhanced for extensive disease after poor preoperative disease control and inadequate surgical treatment, but is reduced after adjuvant chemotherapy. Although they demonstrated that early recurrence negatively affects prognosis, but re-resection may restore better survival. Chemotherapy before early recurrence resection is advocated.

CONCLUSIONS

The addition of biological agents to chemotherapy, such as Beva and Cetux, and the improvements of surgical technics have opened a new scenery in the management of CRC LM, unfortunately with few data in so called frail patients i.e HIV-positive and elderly patients[32-38]. For many years, the diagnosis of LM from CRC was characterized by a dismal prognosis. Chemotherapy and surgery were two worlds which ignored each other. But, in light of the results of the studies cited, the chemotherapy and surgery can finally collaborate. In the unresectable setting the association of chemotherapy with Beva and Cetux is particularly promising in improving resectability rate. In particular, KRAS is a molecular predictive factor that could be particularly useful in selecting the best treatment option in patients with unresectable LM.

Challenges for the immediate future are represented by: the definition of the role of biological agents as neoadjuvants, the assessment of biological markers of response to pre-operative chemotherapy and the assessment of the chemotherapy with best liver toxicity profile[39].

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