Cetuximab and Chemotherapy for Patients with Unresectable CRC Liver Metastasis: Are We Changing the Natural Course of the Disease?

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Colorectal cancer (CRC) is the second most frequent cause of cancer-related death in Europe [1]. Liver metastases are the main cause of death in this patient population. Approximately 20% of patients have liver metastases at the time the primary tumour is diagnosed, and 25% more will develop metastatic lesions in the follow-up after they undergo resection of their primary tumour. For selected patients who have recurrent disease that is confined to the liver, surgical resection of the metastases is the treatment of choice, with a 5-year survival rate of approximately 40% reported in the recent literature [2, 3]. Although there have been substantial advances in the treatment of metastatic CRC (mCRC) median survival remains below 2 years and less than 5% of patients survive for more than 5 years [4–6]. However, chemotherapy can render previously unresectable liver metastases operable, conferring the possibility of curative surgery.

The original experience from the Paul Brousse Hospital in France reported by Bismuth and Giacchetti in patients with initially unresectable mCRC treated with oxaliplatin/5-Fluorouracil (5-FU)/Leucovorin (LV) showed a salvage hepatic resection rate between 16 and 38% [7, 8]. The 5-year survival rate after liver resection in the report by Bismuth et al. was 40%, and the median survival in the report by Giacchetti et al. was 48 months for the patients who underwent resection and 15.5 months in the patients who did not undergo resection. Subsequent trials confirmed the ability of neoadjuvant chemotherapy to render patients resectable. Alberts et al. reported a 62% response rate (RR) in 42 patients with initially unresectable liver metastasis treated with FOLFOX4 and secondary resection was possible in 17 patients (41%). The median survival for the global population of the study was 31.4 months [9]. The encouraging results mentioned above are obtained in these much selected populations of patients with mCRC predominantly with liver metastasis only treated at highly qualified centres with devoted hepatic surgery teams.

Delaunoy et al. evaluated the secondary resection rate among 795 patients treated within the Intergroup Study N9741 this being a more unselected setting in the context of a large cooperative group [10]. 24 patients (3.3%) underwent secondary resections: 2 patients treated with IFL, 11 with FOLFOX4, and 11 with IROX. The median survival was not reached in the resected group at the time of the publication, whereas patients who achieved a partial response but who did not undergo resection had a median survival of 21 months. Globally, these data show that neoadjuvant chemotherapy can potentially render some previously unresectable patients resectable, with the possibility of prolonged survival.

Further improvements in treatment are likely to be facilitated by the use of rationally selected therapeutic agents that target functionally important proteins in tumour cells, such as the epidermal growth factor receptor (EGFR), expressed in 75–89% of CRCs [11]. Cetuximab (Erbix[®], Merck Pharma GmbH, Darmstadt, Germany), an IgG1 monoclonal antibody (MAB) directed to the ectodomain of the EGFR, has demonstrated clear activity, both as a single agent and when combined with irinotecan in mCRC patients who have failed irinotecan-based therapy [12]. Furthermore, the combination of cetuximab with different irinotecan/5-FU/LV regimens has shown an acceptable safety profile and promising RR (43–67%) in the first-line setting [13–16].

In this issue of the journal, Min et al. [17] present the results of a phase II clinical trial designed to investigate the ability of the combination of cetuximab with the chemotherapy schedule of irinotecan, and 5-FU/LV (FOLFIRI) in downsizing initially unresectable mCRC patients with liver metastases. Of the 23 patients enrolled in the study, 9 patients presented an objective response, the RR being 39.1%. Potentially curative resection of liver metastases could be performed in 7 out of the 23 patients included, the secondary hepatic resection rate being 30.4%.

The data of several studies evaluating the combination of cetuximab and irinotecan-based chemotherapy have been recently reported. Folprecht et al. showed the results of a phase I/II clinical trial evaluating the combination of cetuximab and weekly irinotecan/infusional 5-FU/LV (AIO) in non-selected mCRC patients (those with hepatic and/or extrahepatic metastatic disease) [13]. 14 out of 21 patients (67%) achieved an objective response. This activity translated in the possibility of R0 salvage surgery in 4 patients with liver metastases, the hepatic resection rate being 24%. Another study in unselected patients with mCRC treated with cetuximab plus the chemotherapy FOLFIRI regimen showed a 45% RR with 10 (24%) patients being able to have secondary resections, 9 with liver metastasis (8 with R0 resections) [15]. The phase III CRYSTAL study investigated the effectiveness of cetuximab in combination with the standard FOLFIRI regimen compared with FOLFIRI alone in the first-line treatment of unselected patients with EGFR-expressing mCRC [16]. A total of 1,217 patients were included in the study. The addition of cetuximab significantly prolonged progression-free survival, the primary endpoint of the study, and increased the RR (47% vs. 39%, $p < 0.005$). A preliminary exploratory analysis of the study showed a 9.8% R0 hepatic resection rate in the population with only liver metastases treated with FOLFIRI plus cetuximab compared with 4.5% of those treated with FOLFIRI alone.

The combination of oxaliplatin-based chemotherapy plus cetuximab has extensively been evaluated in several phase II/III clinical trials in the first-line setting [18–21]. The initial phase II ACROBAT study [18] of FOLFOX-4 plus cetuximab was conducted in 43 patients showing an unconfirmed RR of 79% and a confirmed rate of 72%. Encouragingly, 10 patients (23%) underwent resection with curative intent of previously unresectable metastases. The resection with curative intent rate of 23% achieved in this study is therefore comparable to

the highest reported for unselected patients [22, 23]. The preliminary results of two randomized phase II studies (CALGB 80203 and OPUS) have been recently presented showing an increase in the RR of patients treated with the combination of cetuximab and FOLFOX-4 compared with those treated with FOLFOX-4 alone [20, 21].

In summary, the present study, as well as other published studies, has provided encouraging information on the possibility of secondary resection of liver metastasis after primary chemotherapy in combination with the anti-EGFR monoclonal antibody cetuximab in patients with initially unresectable liver metastasis. Complete resection of liver metastases in these patients provides the best opportunity for long-term survival. These emerging data show that neoadjuvant treatment can render some initially unresectable patients resectable, hence affording these patients the possibility of cure. Cetuximab seems to add substantial benefit to standard oxaliplatin- and irinotecan-based combinations resulting in high response rates in the first-line setting (up to 72–79%). Cetuximab-based regimens provide a consistently high rate of resectability in the range of 13–24% in unselected patients, these data suggesting that the use of cetuximab combined with cytotoxic therapy early in a patient's treatment course could probably render an important proportion of unresectable mCRC patients resectable. Nevertheless these encouraging results of the neoadjuvant treatment with cetuximab combined with standard chemotherapy in patients with initially unresectable liver metastasis have to be confirmed in the context of randomised trials specifically designed for this selected population of patients. Several randomised phase II studies, like CECOG-612, CELIM-604, EORTC-BOS and TTD-0402, are currently addressing this hypothesis with specific endpoints like the resectability rate, and will hopefully give more light in this challenging clinical setting.

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