

Commentary: randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases

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This study aimed to assess the effect of cetuximab plus chemotherapy as first-line treatment to unresected colorectal liver-limited metastases (CLMs). Study design was the randomized controlled trial to receive chemotherapy (mFOLFOX6 or FOLFIRI) plus cetuximab (arm A) or chemotherapy alone (arm B) for patients with KRAS wild-type synchronous unresectable CLMs (1). This randomized trial conducted that the primary tumor had to be resected before study entry in patients with synchronous liver metastases as the same as the CELIM study. The primary end point was the rate of patients converted to resection for liver metastases. Secondary end points included tumor response and survival. The CELIM study aimed to assess the effectiveness of cetuximab in combination with chemotherapy for unresectable CLMs to downsize tumors for curative resection in the form of a prospective randomized trial (2). The R0 resection rate was 34%. The median overall survival (OS) was 35.7 (95% CI: 27.2-44.2) months and the median progression-free survival (PFS) was 10.8 (95% CI: 9.3-12.2) months. The estimated 3- and 5-year OSs were 48.3% (95% CI: 38.9-57.7%) and 27.5% (95% CI: 18.7-36.3%), respectively. Patients who had undergone a R0 resection had a significantly longer OS [median: 53.9 (95% CI: 35.9-71.9) months] than patients without any resection [21.9 (95% CI: 17.1-26.7) months, HR 0.29, $P < 0.001$]. The median PFS was 15.4 (95% CI: 11.4-19.5) months in patients who had undergone a R0 resection. The 5-year survival rate for R0 resected patients was 46.2% (95% CI: 29.5-62.9%) (3). The CELIM study showed that compared with historical controls, chemotherapy with cetuximab yielded a higher response rate and therefore

increased resectability. However, the lack of a control group makes it difficult to conclude the role of cetuximab in clinical practice. In this study, patients in arm A had increased 3-year OS rate (41% vs. 18%; $P = 0.013$) and prolonged median survival time (MST) (30.9 vs. 21.0 months; $P = 0.013$) compared with those in arm B. The 5-year OS rate has not yet been reached.

The R0 resection rates for liver metastases were 25.7% (18 of 70 patients) in arm A and 7.4% (5 of 68 patients) in arm B, which were significantly different ($P < 0.01$). In the CRYSTAL trial (4), the addition of cetuximab to FOLFIRI resulted in an increase in the resection rate from 4.5% to 9.8% in a subgroup of patients with liver-only disease. Similarly, in the OPUS study (5), the resection rate for liver metastases doubled from 2.4% to 4.7%. The main reason, that R0 resection rate has higher in arm A, is where entry and end points were determined by liver surgeons as the same setting as the CELIM study. This study emphasized the need for the multidisciplinary team approach, especially the input of experienced liver surgeons.

The overall response rate (ORR) were 57.1% in arm A and 29.4% in arm B, which were significant different ($P = 0.022$). The ORR in chemotherapy alone is lower than other reported studies. Poor prognostic factors for patients with liver metastases are multiple metastases, > 5 cm in diameter, synchronous presentation, lymph node-positive primary and high tumor marker levels (6). To be limited to synchronous liver metastases may be associated with lower ORR in chemotherapy alone.

The adverse effects associated with these treatment options include 34% skin reactions in the CELIM study. In

this study, skin toxicity rate was 12.9%. This rate was lower than Crystal study (21%) and OPUS study (18%). However, patients with grade 2 to 3 skin reactions experienced greater benefit than those with grade 0 to 1 skin reactions in terms of ORR. Higher-grade skin toxicities were associated with an improved ORR in agreement with previous studies.

The new EPOC study examined perioperative treatment with chemotherapy plus or minus cetuximab for KRAS wild-type patients with resectable LCMs (7). However, the study showed that the addition of cetuximab to chemotherapy is not beneficial for patients with KRAS wild-type resectable LCMs. The main difference between new EPOC study and this study is including criteria whether resectable or unresectable LCMs. The biological differences between unresectable and resectable LCMs might affect the response to cetuximab in the same way that there might be biological differences between the negative studies in adjuvant setting and the positive studies in the metastatic setting. However, liver metastases were classified as unresectable if they were large in size, poorly located, multi-nodular or there was evidence of extra-hepatic disease, but the criteria differ from one center and another (8-10). In fact, some cases in this study have less than five nodules or <5 cm in diameter, being considered as resectable LCMs, though synchronous liver metastases. Therefore, it is too early to know that the addition of cetuximab to chemotherapy is not beneficial for KRAS wild type patients with resectable LCMs until getting the results of other further clinical trials.

In conclusion, this study played a core role as a prospective randomized trial to confirm the results of the CELIM study. However, this study has some limitations. The number of patients analyzed in a single center setting was limited, and the 5-year OS rate has not yet been reached. The new trials in a multicenter setting using a multidisciplinary treatment approach, including the CELIM2 trial (NCT01802645) and NSABP FC-6 trial (NCT00803647), are needed to establish the addition of cetuximab to chemotherapy in this setting.

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