Editorial

Multidisciplinary approach and targeted agents increase resectability of liver-limited metastases from colorectal cancer

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The outcome of patients with initially unresectable metastatic colorectal cancer have greatly improved in the past years (1) and at least three important factors have certainly contributed: a multidisciplinary approach, the availability of targeted agents and the knowledge of the molecular pathways of metastatic colorectal cancer. On June 2013, Ye *et al*. (2) published on the *Journal of Clinical Oncology* the results of a single-center randomized trial investigating the effect of the addition of cetuximab to first-line chemotherapy for radical resection rate of liver metastases from colorectal cancer. An editorial by N. Kemeny accompanied the paper (1) and, on December 2013, a correspondence between the authors and other international working groups was published on the same journal (3-5). Overall 138 Chinese patients affected by unresectable synchronous liver-limited metastases (LLM) from KRAS wild-type resected colorectal cancer were enrolled and they were randomized to receive anti-EGFR monoclonal antibody Cetuximab plus first-line fluorouracil-based doublets of chemotherapy (FOLFOX or FOLFIRI) or chemotherapy alone as first-line treatment. The mean age of study population was young, nearly 58 years, with 80% of patients with optimal general condition and ECOG performance status 0. The two arms of treatment (cetuximab plus chemotherapy versus chemotherapy alone) were well balanced regarding the motivation of non-resectability; at the same time, the experimental arm had 22% less patients with features indicating a worse prognosis (1). Nearly 30% of patients received the fluorouracil plus irinotecan combination (FOLFIRI) and a further 20% of patients received the sequence of both irinotecan and oxaliplatin-based doublets. One of the most significant aspects of this trial was that resectability was evaluated, before and after treatment, by a multidisciplinary team involving at least three liver surgeons and one radiologist. After treatment, all of the following issues must be present in order to undergo resection:

(I) Capability to obtain a radical resection;
(II) Preservation of at least two contiguous liver segments;
(III) Preservation of adequate vascularization and biliary drainage;
(IV) Preservation of an adequate hepatic function (at least 20% of healthy liver).

At a median follow-up of 25 months, the radical resection rate (RRR) was respectively 25% and 7% in the cetuximab plus chemotherapy and in the chemotherapy alone arms, with an odds ratio in favor of the experimental arm of 4.37 (primary endpoint). Overall survival in the two groups of resected patients was comparable and about 40 months but, unfortunately, nearly 66% of resected patients recurred. Relatively to the safety, adding cetuximab to chemotherapy increased uniquely the occurrence of severe acneiform rash (12.9% versus 2.9%).

The results of this study confirm the concept of "conversion chemotherapy" in which a marked tumoral shrinkage after first-line chemotherapy can lead to the radical resection of liver metastasis with a relevant prolongation of survival, although often the disease will recur. Even in the setting of unresectable metastases, the addition of targeted agents to standard chemotherapy has improved outcomes (6,7) while, on the contrary, when metastases can be initially resected nor "standard" chemotherapy (8) nor addition of Cetuximab (9) have demonstrated to increase OS. Despite encouraging premises, there aren't at the moment randomized multicentric trials able to confirm if chemotherapy plus cetuximab can be considered the standard of care for patients with LLM from resected, KRAS wild

type, colorectal cancer. However the encouraging results of Ye *et al*. (2) about RRR in LLM can be updated by some recent trials conducted in the setting of "conversion chemotherapy. The recent update of the CELIM phase II trial (CEtuximab in neoadjuvant treatment of unresectable colorectal LIver Metastases), conducted on 114 European patients with unresectable LLM, show RRR data comparable between Cetuximab plus FOLFOX and Cetuximab plus FOLFIRI (10). Median OS and progression-free survival for resected patients were comparable to the trial by Ye *et al.* (2). 53 versus 46 months and 10 versus 10.7 months; overall survival at 5 years was 46% in the CELIM trial (10). In a Japanese trial by Kataoka *et al*. (11), 115 patients with LLM and resected primitive carcinoma were treated with the association of chemotherapy with various targeted agents. A multidisciplinary team evaluated resectability and allocated patients to three groups: resectable, "conversion therapy" and unresectable. An overall 18% resection rate was obtained with a statistically different survival between the "conversion" and the unresectable group. However PFS in the "conversion" group was clearly inferior respect to the "resectable" group (3 versus 16 months), thus confirming that the initial extent of the disease remains the more relevant prognostic factor and that respectability is often not equivalent to cure.

Taken together with recent advances in molecular biology, the results of these trials can ameliorate our clinical practice. First, in patients with LLM, the definition of resectability must be performed by a multidisciplinary team involving both liver surgeons and liver radiologists; particularly, the use of second-level imaging techniques mainly magnetic resonance (MR) or positron emission tomography/computed tomography (PET/CT) scan should be strongly considered (12), owing in mind that the potential benefit of a prolonged survival is realistic. Moreover, when resectability is the aim of treatment, the choice of first-line drugs, particularly in KRAS wild-type patients should comprehend, in fit patients, more than a standard doublet FOLFOX/FOLFIRI. The addition of cetuximab is a valid option (1,10) with a toxicity profile involving mainly the skin: in the CELIM trial grade 3-4 skin toxicity was present in 15-22% of patients (13); in the trial by Ye *et al*. in 13% (2). These data are in accord with available literature, from which it appears that these toxicity is in part preventable (14) and in the majority of cases manageable with dedicated algorithms (15). At the same time, recent evidences showed that a comprehensive analysis of both KRAS and NRAS should be performed before treatment with anti-EGFR monoclonal antibodies (7). Moreover a possible role for the analysis of further genes such as BRAF, PIK3CA and PTEN is under evaluation (16). Facing such complexity, tools able to perform molecular analysis during chemotherapy, like for example, liquid biopsy of circulating tumor DNA, could be in the future fundamental elements in order to personalize the treatment (17).

It is not clear if a chemotherapy with three drugs is better than the association of cetuximab plus FOLFOX/FOLFIRI. The FOLFOXIRI triplet (fluorouracil/irinotecan/oxaliplatin) showed an overall 36% RRR in patients with LLM, superior to those from the trial by Ye *et al*. (2) and the CELIM trial (10), but with a clear increase in toxicities, especially hematological and neurological (18). Recent data from the TRIBE (Combination Chemotherapy and Bevacizumab as First-Line Therapy in Treating Patients With Metastatic Colorectal Cancer) trial showed that the addition of bevacizumab to FOLFOXIRI probably has no effect on resectability (19). Regarding the addition of Cetuximab to FOLFOXIRI, to date only small phase II trials are available, showing the feasibility of these combination with resection rates superior to 30% (20,21). Furthermore, when considering the continuum of care of patients, the use of a doublet, respect as a triplet, has the advantage that the remaining non-cross resistant doublet can be utilized as second-line chemotherapy.

In conclusion, when facing a relatively young and healthy patient affected by LLM from colorectal cancer, RAS (and possibly BRAF) wild-type, only after a multidisciplinary and multi-imaging evaluation of non-resectability with at least CT scan and MR or PET/CT, the treatment with the association of cetuximab with fluorouracil-based doublets should be strongly considered. We can in fact expect the conversion to resectability in up 25% of patients with, in this case, a prolonged survival in 30-50% of patients. Lacking phase III trials in this setting, it is advisable that new multicentric trials will analyze these aspects (22,23) and that new molecular techniques con improve the personalization of treatments in the various subgroups of patients (16,17).

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