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LETTER TO THE EDITOR

Is post-transplant chemotherapy feasible in liver transplantation for colorectal cancer liver metastases?

Dear Editor:

In the last two decades, the indications of liver transplantation (LT) for primary and secondary hepatobiliary malignancies have been increasingly expanded. Although this attractive option still represents the "last court of appeal" in cancer patients, the role of LT is well established in hepatocellular carcinoma (HCC), where transplantation has also demonstrated a benefit for selected patients affected by peri-hilar cholangiocarcinoma, intrahepatic cholangiocarcinoma, and neuroendocrine tumors [1].

Recently, the interest in LT in liver-limited stage IV colorectal cancer (CRC) has increased due to recent advances in transplantation techniques that have led to a re-evaluation of this approach. Encouraging data from small studies and series have demonstrated an overall survival (OS) at 5 years between 50% and 83% in transplant patients, bringing new light on LT in CRC [2-4]. Nevertheless, few data support the use of post-transplant chemotherapy in this setting, given the small number of patients who underwent LT for non-resectable colorectal liver metastases (NRCLM) and the lack of prospective studies comparing LT with the current standard of care. Another controversial issue concerns the possibility to administer or not post-transplant chemotherapy concurrently with immunosuppressive therapy and its role in improving survival in these patients [5].

To our knowledge, there are no published series reporting the administration of postoperative chemotherapy in CRC after LT. We herein report three patients affected by NRCLM who underwent LT and received postoperative treatment with intensive chemotherapy schedules. In each case, the decision to perform LT was taken after discussion of the multidisciplinary team and ethical committee (IRB) approval, considering the young age of the patients, the expected median OS with standard therapeutic options available, and ineligibility in clinical trials. Last follow-up was December 2019.

The first patient, a forty-year-old man, had a colonoscopy following a three-month history of constipation and he was diagnosed in September 2013, with unresectable liver metastases of KRAS wild-type colon cancer. Starting from October 2013, first-line chemotherapy combining FOLFOX (folinic acid, fluorouracil, and oxaliplatin) and anti-VEGF (vascular endothelial growth factor) monoclonal antibody (bevacizumab) was administered for 12 cycles with a remarkable radiographic response, then maintenance with bevacizumab was given for another 6 cycles. A restaging computed tomography (CT) scan showed a liver-limited disease progression, so the patient received a second chemotherapeutic treatment with FOLFIRI (folinic acid, fluorouracil, and irinotecan) and anti-EGFR (Epidermal growth factor receptor) monoclonal antibody (cetuximab) for 8 courses, and achieved stable disease. Thus, in December 2014 a left hemicolectomy was performed without extended hepatectomy because of the inadequate hepatic functional reserve. The same chemotherapy schedule was continued for 13 courses with stable disease as best response up to July 2015, when our patient underwent LT from a deceased donor. Postoperative chemotherapy with FOLFOX was administered along with tacrolimus, everolimus, and prednisone for 6 cycles, during which our patient experienced thrombocytopenia G1, gastrointestinal toxicity G1 and paresthesia G2 that led to oxaliplatin discontinuation after three courses. In May 2016, after eight months from LT, a positron emission tomography (PET) scan showed a sub-centimeter (diameter 0.8 cm) nodule with slight F-18 fluorodeoxyglucose (FDG) uptake (SUV_{max} = 2.5) in the right lower lobe lung, whose malignancy was confirmed by pulmonary metastasectomy. Subsequently, the patient was strictly followed-up for three years until May 2019, when a low FDG uptake was detected in the retrocaval lymph nodes. From June to August 2019, the patient received chemotherapy with FOLFOX for 4 cycles, then he underwent stereotactic body-radiotherapy (SBRT)

to retrocaval lymph nodes. To date, the patient is in an acceptable general condition without any evidence of disease (Supplementary Figure 1).

In August 2015, second patient, a fifty-nine-year-old man, presented with synchronous and multiple liver metastases from RAS (Ras Oncogene) and BRAF (proto-oncogene B-Raf) wild-type rectosigmoid adenocarcinoma. The diagnosis was followed by a positive fecal occult blood test, as a part of a health screening program. In September 2015, the patient started systemic treatment with FOLFOXIRI (folinic acid, fluorouracil, oxaliplatin, and irinotecan) and bevacizumab for 14 cycles. In June 2016, he underwent left hemicolectomy with lymph node dissection, while the presence of liver metastases was confirmed intraoperatively. From the perspective of LT, the treatment was continued for an additional 6 cycles, burdened with neutropenia G2 and paresthesia G1. Since PET imaging showed stable disease with no extra-hepatic dissemination, in November 2016 the patient received a right liver graft from living donor without complications. Thereafter, in January 2017 post-operative FOLFOXIRI was concurrently treated with prophylactic lamivudine because of HBcAb-positive organ donor; immunosuppression protocol consisting of tacrolimus and corticosteroids were administered during the systemic treatment. After 6 courses of FOLFOXIRI, the only adverse event reported was afebrile neutropenia G4. From July 2017, the patient underwent two atypical lung resections of the right lower lobe (1.2 cm in diameter) and the left upper lobe (0.9 cm in diameter) respectively after the evidence of dimensional increase of pulmonary nodule. In September 2019, a third pulmonary metastasis was detected by CT scan and was successfully treated with stereotactic body radiotherapy (SBRT). In October 2019, a new PET scan showed hypermetabolic left hilar lymph nodes with a SUV_{max} of 8 and, at the same time, and the patient's CEA (carcinoembryonic antigen serum level was found to increase from 1.4 (August 2019) to 7.4 ng/mL (October 2019). At the last follow-up in December 2019, the patient was receiving FOLFOX and anti-EGFR monoclonal antibody (panitumumab) regimen (Supplementary Figure 2).

The third patient, a forty-seven-year-old man, was initially diagnosed with bilobar synchronous liver metastases from rectal adenocarcinoma, KRAS wild-type, which were incidentally found on abdominal ultrasonography. Starting in November 2015, the first chemotherapeutic treatment was given using FOLFOX, and panitumumab for 12 cycles with good tolerance, obtaining a partial response; therefore, in June 2016 the patient received abdominoperineal resection of the rectum (Miles' resection). Two months later, initial hepatic resection limited to three metastases was performed as the risk of small future liver remnant volume did not allow extended hepatectomy. The CT restaging showed liver disease progression with suspicious enlarged inter-aortocaval lymph node, which was no more detected on the following imaging. Following 12 cycles of second-line chemotherapy with FOLFIRI and bevacizumab from October 2016 to May 2017, he underwent LT from a heart-beating donor in June 2017. The following month the patient was re-hospitalized for acute fever with no identifiable cause and during this time he had a chest CT scan that showed a sub-centimeter pulmonary nodule in the left lung. Even then, postoperative chemotherapy with FOLFOX was administered for 6 courses along with tacrolimus, everolimus, and prednisone from August to November 2017. The persistence of neutropenia G3 led to the discontinuation of everolimus after 4 cycles. In January 2018, CT and PET scan revealed a dimensional increase of lung metastases, which were treated with FOLFIRI and bevacizumab schedule for 15 cycles. In October 2019, complete surgical resection of the pulmonary metastases was performed, which comprised of culmenectomy and inferior bilobectomy of 3 nodules of 1.7, 1.6 and 2 cm in diameter, respectively. Finally, the patient is alive and under active surveillance without any evidence of disease postoperatively (Supplementary Figure 3).

Previous findings from SECA I, SECA II, and the multicenter retrospective cohort study published by Toso et al [2–4] have provided encouraging evidence in favor of upfront chemotherapy in potential transplant candidates. These studies have also assessed response to chemotherapy as a good prognostic factor, while the role of post-transplant chemotherapy and its interaction with immunosuppressive protocols has not been clarified yet [2–4]. Life-long immunosuppressive therapy is known to expose solid organ transplant recipients to a higher risk of malignancy when compared to the general population as well as disease progression [6]. Cyclosporine and tacrolimus may play a role in upregulating of VEGF and increasing the expression of TGF-β1 (Transforming growth factor-beta 1), which in turn may facilitate angiogenesis, cancer cell invasion, and metastasis. On the other hand, there has been evidence to support the effect of mTOR inhibitors sirolimus and everolimus on cancer prevention [7, 8].

Similarly, in HCC, post-operative systemic treatment post-LT lacks robust evidence [9]. In 2015, a meta-analysis by Lin et al evaluated the role of adjuvant chemotherapy post-LT in HCC patients, demonstrating a benefit in terms of overall survival [Hazard Ratio (HR): 0.34; 95% Confidence Intervals (CI): 0.22-0.52; $P < 0.001$] and disease-free survival (HR: 0.87; 95% CI: 0.78-0.95; $P = 0.004$); unfortunately, the quantitative analysis of adverse events was not possible because of the anecdotal nature of the data collected, but the incidence of severe adverse events seemed

TABLE 1 Outcomes and adverse events related to pre- and post-transplant chemotherapy

Patient	Schedule pre-LT	AE pre-LT	Liver functionpre-LT	CEA pre-LT (μ/L)	Schedule post-LT	AE post-LT	Immuno-suppressive drugs during post-LT chemotherapy	OS after LT (months)	DFS after LT (months)
1	FOLFOX+ beva	Rash (G1), Nausea (G2), Vomit (G1), Paresthesia (G1)	Alb 3 g/dL, AST 51 U/L, ALT 46 U/L, Bil 0.7 mg/dL, GGT 50 U/L, ALP 140 U/L, PT 0.95	82	FOLFOX → 5-FU	Thrombo-cytopenia G1, Nausea G1, Vomit G1, Dysgeusia G1, Paresthesia G2	Tacrolimus + Everolimus + Prednisone	53	8
2	FOLFOXIRI + beva	Neutropenia (G2), Paresthesia (G1)	Alb 3.2 g/dL, AST 63 U/L, ALT 47 U/L, Bil 1 mg/dL, GGT 80 U/L, ALP 190 U/L, PT 0.98	58	FOLFOX-IRI	Neutropenia G4	Tacrolimus + Prednisone	37	8
3	FOLFOX + pani	Neutropenia G2, Rash G1, Paresthesia G2	Alb 4 g/dl,L AST 61 U/L, ALT 83 U/l, Bil 0.4 mg/dL, GGT 40 U/L, ALP 120 U/L, PT 1.1	94	FOLFOX	Neutropenia G3	Tacrolimus + Everolimus + Prednisone → Tacrolimus + Prednisone	29	7

Abbreviations: beva = bevacizumab; pani = panitumumab; alb = serum albumin; AST = alanine transaminase; ALT = aspartate transaminase; bil = total bilirubin; GGT = gamma-glutamyltransferase; ALP = alkaline phosphatase; PT = Prothrombin time; OS = overall survival (defined as time from LT to end of follow-up); DFS = disease-free survival (defined as time from LT to suspected metastatic lesions or local relapse described by CT/magnetic resonance imaging/positron emission tomography-scans); LT = liver transplant; AE = adverse events; Toxicity data were classified according to the CTCAE (Common Terminology Criteria for Adverse Events) version 4.

to be low and included myelosuppression, neurotoxicity, and infection [10].

Although based on a smaller number of patients, our initial experience suggests that post-transplant chemotherapy including cytotoxic doublet or triplet (e.g. FOLFOX, FOLFOXIRI) may represent a safe approach in patients who underwent LT for NRCLM, even if systemic treatment is administered within a few weeks after surgery. We chose post-transplant treatment for each patient by administering the same standard-schedule or the same de-escalate schedule that achieved the best radiological response in the previous lines of chemotherapy; consequently, we noted that adverse events reported during post-transplant chemotherapy did not differ greatly from the ones reported in pre-transplant treatment (Table 1). According to our experience, the concomitant administration of immunosuppressive protocols did not seem to interfere with compliance to chemotherapy (Supplementary Table). In the case of G3-G4 neutropenia, for instance, it was possible to reduce up to 30% the dose of adjuvant chemotherapy or to modify the standard immunosuppression protocol rather than discontinue the treatment.

Nevertheless, the question of whether post-transplant chemotherapy could have an impact on survival of patients with NRCLM remains unclear and our results should be interpreted with caution, due to the descriptive nature of the series and the inclusion of only three cases. We believe our results may act as an incentive for designing prospective multi-center RCTs that aim at assessing the efficacy of post-transplant chemotherapy in this nearly unexplored setting.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All patients provided written informed consent for publication of this paper

CONSENT FOR PUBLICATION

All patients provided written informed consent for publication of this paper.

POTENTIAL CONFLICT OF INTEREST

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