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, intra-hepatic 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 hemicolec- tomy 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 (SUVmax = 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 SUVmax 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 FOLFIRI, 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 heptec-
TABLE 1

| Patient | Schedule post-LT | AE post-LT | Liver function pre-LT | CEA (µ/L) |
|---------|------------------|-----------|-----------------------|-----------|
|         |                  |           |                       |           |
| 1       | FOLFOX + beva    | Rash (G1), Nausea (G2), Vomil (G1), Paresthesi (G1) | Alb 3.2g/dL, AST 63 U/L, ALT 83 U/L, Bil 0.4mg/dL, GGT 40 U/L, ALP 120 U/L, PT 1.1 | 29        |
| 2       | FOLFOX + beva    | Thrombo-cytopenia, Rash (G1), Nausea (G2), Vomil (G1), Paresthesi (G1) | Alb 3.2g/dL, AST 63 U/L, ALT 83 U/L, Bil 0.4mg/dL, GGT 40 U/L, ALP 120 U/L, PT 1.1 | 44        |
| 3       | FOLFOX + panitumumab | Neutropenia (G3), Rash (G1), Paresthesi (G2) | Alb 3.2g/dL, AST 63 U/L, ALT 83 U/L, Bil 0.4mg/dL, GGT 40 U/L, ALP 120 U/L, PT 1.1 | 54        |

Abbreviations: beva = bevacizumab; pan = panitumumab; al = albumin; ast = asthenia; bil = bilirubin; ggt = gamma-glutamyltransferase; alp = alkaline phosphatase; pt = prothrombin time; os = overall survival; dfs = disease-free survival; 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
Nothing to report.

FUNDING
No funding to report.

ACKNOWLEDGMENTS
Nothing to report.
AUTHORS’ CONTRIBUTIONS
All the authors made contributions to the conception, drafting, drawing and final revision.

Giovanni Brandi
Angela Dalia Ricci
Alessandro Rizzo
Chiara Zanfi
Simona Tavolari
Andrea Palloni
Stefania De Lorenzo
Matteo Ravaioli
Matteo Cescon

1 Department of Experimental, Diagnostic and Specialty Medicine, S. Orsola-Malpighi University Hospital, Bologna 40138, Italy
2 Department of General Surgery and Transplantation, S. Orsola-Malpighi University Hospital, Bologna 40138, Italy
3 Center of Applied Biomedical Research, S. Orsola-Malpighi University Hospital, Bologna 40138, Italy

Correspondence
Angela Dalia Ricci, Department of Experimental, Diagnostic and Specialty Medicine, S. Orsola-Malpighi University Hospital, Bologna, Italy. Email: dalia.ricci@gmail.com

ORCID
Angela Dalia Ricci https://orcid.org/0000-0002-0701-6764

REFERENCES
1. Schaefer B, Zoller H, Schneeberger S. Con: Liver transplantation for expanded criteria malignant diseases. Liver Transpl. 2018;24(1):104-111.
2. Hagness M, Foss A, Line PD, Scholtz T, Jørgensen PF, Fosby B et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg 2013;257(5):800-806.
3. Dueland S, Syversvæn T, Solheim JM, Solberg S, Grut H, Bjørnbeth BA et al. Survival Following Liver Transplantation for Patients With Nonresectable Liver-only Colorectal Metastases. Ann Surg. 2020;271(2):212-218.
4. Toso C, Pinto Marques H, Andres A, Castro Sousa F, Adam R, Kalil A et al. Liver transplantation for colorectal liver metastasis: Survival without recurrence can be achieved. Liver Transpl. 2017;23(8):1073-1076.
5. Abreu P, Gorgen A, Oldani G, Hibi T, Sapisochin G. Recent Advances in Liver Transplantation for Cancer: The Future of Transplant Oncology. JHEP Rep 2019;1(5):377-391.
6. Simoneau E, D’Angelica M, Halazun KJ. Liver transplantation for colorectal liver metastasis. Curr Opin Organ Transplant 2019;24(2):175-18.
7. Toso C, Merani S, Bigam DL, Shapiro AMJ, Kneteman NM. Sirolimus-based immunosuppression is associated with increased survival after liver transplantation for hepatocellular carcinoma. Hepatology. 2010;51(4):1237-1243.
8. Opelz G, Unterrainer C, Süsal C, Döbler B. Immunosuppression with mammalian target of rapamycin inhibitor and incidence of post-transplant cancer in kidney transplant recipients. Nephrol Dial Transplant. 2016;31(8):1360-1367.
9. Verna EC, Patel YA, Aggarwal A, Desai AP, Frenette C, Pillai AA et al. Liver transplantation for hepatocellular carcinoma: Management after the transplant. Am. J. Transplant. 2019;20(2):333-347.
10. Lin HS, Wan RH, Gao LH, Li JF, Shan RF, Shi J. Adjuvant chemotherapy after liver transplantation for hepatocellular carcinoma: a systematic review and a meta-analysis. Hepatobiliary Pancreat Dis Int. 2015;14(3):236-245.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.