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 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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Schedule pre-LT</th>
<th>AE pre-LT</th>
<th>Liver function pre-LT</th>
<th>CEA pre-LT (µ/L)</th>
<th>Schedule post-LT</th>
<th>AE post-LT</th>
<th>Immuno-suppressive drugs during post-LT chemotherapy</th>
<th>OS after LT (months)</th>
<th>DFS after LT (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FOLFOX + beva</td>
<td>Rash (G1), Nausea (G2), Vomit (G1), Paresthesia (G1)</td>
<td>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</td>
<td>82</td>
<td>FOLFOX → 5-FU</td>
<td>Thrombo-cytopenia, G1, Nausea G1, Vomit G1, Dyseusia G1, Paresthesia G2</td>
<td>Tacrolimus + Everolimus + Prednisone</td>
<td>53</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>FOLFOXIRI + beva</td>
<td>Neutropenia (G2), Paresthesia (G1)</td>
<td>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</td>
<td>58</td>
<td>FOLFOX-IRI</td>
<td>Neutropenia G4</td>
<td>Tacrolimus + Prednisone</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>FOLFOX + pani</td>
<td>Neutropenia G2, Rash G1, Paresthesia G2</td>
<td>Alb 4 g/dL, AST 61 U/L, ALT 83 U/L, Bil 0.4 mg/dL, GGT 40 U/L, ALP 120 U/L, PT 1.1</td>
<td>94</td>
<td>FOLFOX</td>
<td>Neutropenia G3</td>
<td>Tacrolimus + Everolimus + Prednisone</td>
<td>29</td>
<td>7</td>
</tr>
</tbody>
</table>

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.

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 within a few weeks in patients who underwent LT for NRCLM, even if the initial experience is low and included myelosuppression, neurotoxicity, and infection [10].

Acknowledgments:

Nothing to report.

Funding:

Nothing to report.

Conflict of Interest:

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

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