French Editorial Commentary from the ACHBPT

Transplantation for colorectal liver metastases: lessons from TransMet and future challenges

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The TransMet trial is a multicenter, prospective, randomized controlled study aimed at comparing the efficacy of liver transplantation combined with chemotherapy (LT + CT) versus chemotherapy (CT) alone in patients with unresectable colorectal liver metastases (CRLM) (1). Patient enrollment took place between February 2016 and July 2021. This study enrolled patients aged 18 to 65 years with liver-confined metastases who demonstrated either a partial response or disease stabilization after at least 3 months of CT. The primary objective of the study was to assess 5-year overall survival (OS), with secondary outcomes including 3-year OS, 3- and 5-year progression-free survival (PFS), as well as recurrence rates.

Of the 157 patients assessed for eligibility, 94 were randomized into two groups: 47 received liver transplantation (LT) combined with CT, and 47 continued CT alone. In both groups, 49% (LT + CT) and 47% (CT) of patients had more than 20 liver lesions, with a median maximum tumor diameter of 55 mm in the LT + CT group and 50 mm in the CT group. The median carcinoembryonic antigen (CEA) level was 305 ng/mL for the LT + CT group and 81 ng/mL for the CT group. Following CT, 57% of patients in both groups showed a partial response.

In the LT + CT group, 11 patients did not receive LT despite being assigned: 9 due to hepatic or extrahepatic progression during the waiting period, 1 due to progression during the transplantation process, and 1 due to an interval of more than 3 months between the last CT and the transplantation.

In the intention-to-treat (ITT) analysis, the 5-year OS was 56.6% [95% confidence interval (CI): 43.2–74.1%] for the LT + CT group compared to 12.6% (95% CI: 5.2–30.1%) for the CT-only group, with a hazard ratio (HR) of 0.37 (P=0.0003). In the per-protocol analysis, which included 36 patients from the LT group and 38 from the CT group, the 5-year OS was 73.3% for the LT group and 9.3% for the CT group. The 5-year PFS reached 19.9% and the recurrence rate was 72% in the LT + CT group.

Furthermore, 80% of LT patients experienced at least one severe adverse event (Clavien-Dindo >3b), mainly consisting of biliary and pulmonary complications. These findings highlight a significant survival benefit of LT combined with CT for a selected population of patients with unresectable CRLM, supporting the integration of this approach into the therapeutic standard for these complex cases.

In the current context of managing unresectable CRLM, CT remains the cornerstone of treatment, offering response rates ranging from 54% to 80% depending on protocols combined with targeted agents (2,3). However, the conversion rate to curative surgery remains limited, ranging from 26% to 38% (3). The recent interest in LT in this context is supported by landmark studies such as SECA-I and SECA-II, which demonstrated impressive 5-year survival rates of 60% and 83%, respectively, in highly

selected patients (4,5).

TransMet, the first multicenter prospective trial comparing LT combined with CT to CT alone, represents a significant advancement. The methodological rigor of this study, including strict inclusion criteria and evaluation by an independent committee, reduces patient heterogeneity and selection bias. The prioritization of grafts, enabling rapid LT (within 2 months after CT), helped minimize the risk of tumor progression during the waiting period, a critical factor for the success of this strategy.

One of the notable findings of TransMet lies in the observed survival rates: in the ITT analysis, the 5-year OS is 56.6% for the LT + CT group, compared to 12.6% for the CT-only group (P=0.0003). In the per-protocol analysis, these rates increase to 73.3% in the LT + CT group, highlighting the curative potential of this approach for rigorously selected patients. In the CT group, seven patients unexpectedly benefited from hepatic resection following a favorable response, indicating that for some patients, curative surgery remains a possibility after an optimal response.

The shortage of organs remains a major obstacle. Despite prioritization, 19% of patients (9 in total) were removed from the waiting list due to disease progression, highlighting the challenges of rapid access to transplantation in a context where the average waiting time often exceeds 12 months, as seen in France (6). Nonetheless, this delay could sometimes help identify patients with rapidly progressing disease, thus serving as a "selection criterion" to optimize the use of available grafts.

By comparison, the SECA studies in Norway benefited from shorter waiting times and greater graft availability, which could partially explain the better survival rates observed in these cohorts. In this context, the potential use of living donor grafts could represent an interesting solution to overcome organ shortages and improve access to LT. This approach would also allow better coordination between CT and LT, reducing waiting times and thereby offering improved disease control before transplantation. However, prioritizing grafts for rapid LT also raises ethical and practical questions, particularly regarding its application on a larger scale. In particular, it prompts debates about fairness in the context of organ shortages, especially in relation to other pathologies that already benefit from prioritization. This reflection becomes even more necessary as this prioritization could extend beyond the TransMet study, requiring a balance to be struck between individual benefits and systemic challenges.

Another essential aspect to discuss is post-transplant recurrence, as 72% (n=26) of patients in the LT + CT group experienced recurrence, primarily in the lungs (n=14). Data from the Oslo group report a median survival after recurrence of 37 months, emphasizing that post-transplant recurrence remains a major clinical challenge requiring tailored management and optimized follow-up strategies (7). Additionally, the emergence of distant lesions in this immunosuppressed population raises questions; however, it has been demonstrated that patients treated with LT for unresectable CRLM have a favorable prognosis after pulmonary metastasectomy, with tumor doubling times similar to non-transplanted patients, suggesting that immunosuppression does not accelerate the growth of pulmonary metastases (8). Biological selection of patients is crucial in the treatment of unresectable CRLM. Alterations in signaling pathways, including p53, RTK-RAS, TGFβ, and Notch, as well as specific genes such as *TP53*, *RAS/BRAF*, *SMAD4*, and *FBXW7*, are associated with reduced OS (9). Consequently, certain LT protocols for metastatic diseases currently consider these mutations (10). Moreover, the detection of circulating tumor DNA (ctDNA) appears to be a promising tool for postoperative monitoring, allowing for the early identification of patients at high risk of recurrence and enabling therapeutic strategies to be adjusted accordingly (11).

Regarding the immunosuppression protocol, it initially included methylprednisolone, tacrolimus, and mycophenolate mofetil, later evolving to the introduction of mTOR inhibitors. These adjustments could potentially play a role in managing recurrence. Additionally, the administration of adjuvant CT post-transplantation, although left to the discretion of the oncologist, could also represent a strategy to extend survival and reduce recurrence.

In parallel, new immunotherapies, currently in clinical trial phases, show promising results and could transform the therapeutic landscape for CRLM, paving the way for combined approaches (12). The majority of CRLM are "mismatch repair proficient" (pMMR), as observed in the TransMet study, where 100% of patients in the LT + CT group and 98% in the CT group exhibited this status. This characteristic makes these tumors less responsive to conventional immunotherapies targeting programmed cell death 1/programmed death-ligand 1 (PD-1/PD-L1) (13). However, recent advances suggest potential solutions. Phase II studies have shown that combinations of immunotherapies could induce antitumor activity in

microsatellite stable (MSS) patients (14). These preliminary findings highlight the importance of further exploring these combinations to expand immunotherapy to MSS patients, potentially redefining treatment strategies for this population.

In conclusion, the TransMet study represents a significant advancement in exploring LT for unresectable CRLM. Despite encouraging results, adjustments in patient selection, improved management of complications, and optimization of post-transplant treatments are necessary to refine this strategy and maximize its benefits in the context of CRLM.

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