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## **The Safety and Feasibility of Adjuvant Immunotherapy with Autologous Cytokine-Induced Killer Cells for Patients with Hepatocellular Carcinoma Beyond Milan Criteria after Liver Transplantation**

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**Introduction:** Adjuvant immunotherapy with autologous Cytokine-Induced Killer (CIK) cells has shown promise post-surgery, yet research concerning hepatocellular carcinoma (HCC) patients post-liver transplantation remains sparse. This scarcity is in part due to the immunosuppressive therapy required post-transplantation, which may elevate the risk of acute cellular rejection, potentially diminishing the efficacy of immunotherapy. Furthermore, the generally lower recurrence rate post-transplantation within the Milan criteria complicates the verification of immunotherapy's efficacy in relation to HCC.

**Methods:** This study included HCC patients who exceeded the Milan criteria, selected from two large-volume tertiary hospitals in Korea. Immune cell subsets including NK cells, CD8 TCM, CD8 TEM, CD8 nave cells, MDSCs, Tregs, and CD69 T cells, along with immune markers such as perforin, granzyme, INF-gamma, and TNF-alpha were analyzed pre- and post-CIK therapy.

**Results:** A comparative analysis was carried out between patients who received CIK therapy and those who did not, with a focus on rejection, recurrence-free survival rates, and overall survival rates. Although there were no significant differences in rejection or safety between the groups, the group receiving CIK therapy demonstrated promising improvements in both survival and recurrence rates. The better outcome in patients with immunotherapy is due to the anti-tumor immune environment for suppressing the tumor recurrence according to the immune cell subsets analysis(Figure).

**Conclusion:** CIK therapy could be a safe option for HCC patients who exceed the Milan criteria and undergo liver transplantation. The therapy appears to contribute to an anti-tumor environment and lower recurrence rates, presumably by influencing various immune cells and their functions. Given the small experimental group size, these findings should be interpreted as preliminary, necessitating further validation in larger cohorts. Future studies are warranted to deepen the understanding of CIK therapy's mechanisms, particularly its correlation with improved patient outcomes in the context of specific immune markers.