Evidence for the Immunosuppressive Potential of Calcineurin Inhibitor-Sparing Regimens in Liver Transplant Recipients with Impaired Renal Function

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Patients requiring liver transplantation (LT) frequently experience renal insufficiency (RI), which affects their survival. Although calcineurin inhibitor-sparing immunosuppressive regimens (CSRs) are well known to prevent RI, the immune state in recipients receiving CSR remains to be intensively investigated. In the present study, we investigated the immune state in liver transplant patients suffering from RI who received a CSR comprising a reduced dose of calcineurin inhibitor (CNI), methylprednisolone, and mycophenolate mofetil (MMF). For monitoring the immune-state response to anti-donor allostimulation in these patients, we employed a mixed lymphocyte reaction (MLR) assay using an intracellular carboxyfluorescein diacetate succinimidyl ester (CFSE)-labeling technique.

Among 60 cases of living-donor LT at our institute, 68% of the patients had none to mild RI (non-RI group) and 32% of the patients had moderate to severe RI (RI group). The RI group received a CSR comprising reduced dose of tacrolimus, methylprednisolone, and MMF, while the non-RI group received a regimen comprising conventional dose of tacrolimus and methylprednisolone. One year after LT, the mean estimated glomerular filtration rate (eGFR) in the non-RI group had significantly deteriorated. In contrast, the mean eGFR in the RI group had significantly improved after LT, although it was still lower than that of the non-RI group. Notably, 53% of the patients in the RI group were completely cured of RI by 1 year after LT. None of the patients had severe RI at 1 year after LT nor required chronic hemodialysis during the observation period.

Serial mixed lymphocyte reaction assays revealed that anti-donor T cell responses were adequately suppressed in both groups. To evaluate the immune status of these patients, we employed a serial MLR assay using a CFSE-labeling technique. In both groups, limited CD4+ and CD8+ T-cell proliferation was observed in the anti-donor responses as compared with the anti-third-party responses through the first year. At 1 month after LT, the average of stimulation index (SI) for CD4+ T cells in response to anti-third-party stimulation was >2 (the average value in healthy volunteers without any immunosuppressive treatment) i.e., there was a normal response in the anti-third-party.

At 1 year after LT, the average of SIs for CD4+ and CD8+ T cells in response to both anti-donor and anti-third-party stimulation was <2. There were no significant differences in acute rejection rates, bacterial, fungal, or cytomegalovirus infection rates and patient survival between the groups. In conclusion, patients with pre-transplant RI receiving CSR under immunological monitoring using an MLR assay were associated with less impairment of renal function without an increased frequency of rejection or patient survival. Anti-donor T cell responses were adequately suppressed in these patients as well as in patients who received the conventional immunosuppressive regimen comprising a standard dose of CNI.

Factors Influencing Survival after Liver Transplantation for Colorectal Liver Metastases

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Background: In a prospective trial for Liver Transplantation (LT) for non-resectable colorectal liver metastases (CLM), Kaplan Meier estimates for 2 and 5 years overall survival were 89% and 60% respectively. (n=21).

The patient population was heterogeneous regarding type and T and N stage of primary tumor, hepatic tumor load, lines of chemotherapy received and response to treatment.

Aim: Prognostic factors were identified in order to develop patient selection strategies for LT for CLM.

Methods: Subgroup analyses of the study population were performed

Results: The diameter of the largest hepatic tumor prior to LT, primary cancer surgery less than two years before LT, elevated CEA pre-LT and progressive disease at time of LT were significantly associated with inferior survival. A simple prognostic scoring system containing these factors showed significant association with survival (Figure 1).

Conclusion: Our results suggest that with systematic implementation and refinement of prognostic factors, long-term survival after LT for CLM has potential to reach the level of survival as after first time LT for established indications.

Figure: Preoperative Factors Affecting Survival.

The 16 first patients in the study who had observational time of more than 2 years or who died within this period were analyzed. Panel A shows Kaplan-Meier (KM) plots for patients with maximum tumor diameter above and below the median diameter, 5.5 cm. Panel B shows KM plots for patients with time from primary surgery to LT more than and less than 2 years. Panel C shows KM plots with carcinoembryonic antigen (CEA) levels prior to transplantation above and below 80 μg/L. In panel D patients that had progressive disease (PD) on chemotherapy at time of LT are plotted against patients with stable disease (SD) or who had partial response to chemotherapy (PR).

A prognostic score (PS) ranging from 0 to 4 was established by giving each of the factors in panels A to D a value of 0 or 1 and adding them together. Panel E displays KM plots of these groups of PS. Log rank method is used for calculation of p in all panels.

[Figure 1]