

Optimal Immunosuppression before and after HCC Recurrence

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Introduction

Immunosuppression plays a critical role for a successful liver transplantation (LT), but it is known to increase tumor aggressiveness following recurrence of hepatocellular carcinoma (HCC). Patients with recurrent HCC following liver transplantation fair far less compared to those after resection and immunosuppression has been regarded as the possible cause. The characteristics of immunosuppressants used in LT, their impact on the behavior of HCC, followed by the some clinical results will be discussed.

Characteristics of Immunosuppressants

1. Steroid

Steroid is known to increase skin cancer and Kaposi sarcoma, but it is also known to attenuate the growth of tumors of the lymphatic system like lymphoma. Not much is known about its influence on HCC. Since most of the LT protocols taper the steroid within 6 months, it is most probable that its impact on recurrence of HCC will be limited.

2. Mycophenolate mofetil

In animal studies, mycophenolate mofetil (MMF) was shown to inhibit growth of tumor cells and according to the UNOS data, used of MMF reduces de novo cancers following transplantation. However, there are very few evidences to support that it directly inhibits the growth of HCC both in vitro and in vivo.

3. Calcineurin inhibitors (CNI) - cyclosporine and tacrolimus

Cyclosporine is known to inhibit the repair mechanism of DNA of lymphocytes and increases the ex-

pression of transforming-growth factor beta (TGF- β), which is involved in the appearance of invasive phenotype of cancer cells, and of vascular endothelial growth factor (VEGF), a strong inducer of angiogenesis. Similar pro-oncogenic character was shown with tacrolimus. The CNI immunosuppressants are probably the main cause of aggressive tumor behavior following recurrence of HCC after LT.

4. mTOR (mammalian-target of rapamycin) inhibitors - sirolimus & everolimus

mTOR inhibitors inhibits the proliferation of cells by binding to mTOR receptor and inactivates the intracellular kinase pathway involved in the progression of the cell cycle from the G1 to the S phase. It has also been shown to interfere with various steps of cancer proliferation, cell transformation, and metastasis. Most peculiar, however, is its ability of inhibit angiogenesis by decreasing VEGF production at the concentration of the drug used clinically for immunosuppression.

Impact of Immunosuppression on Recurrence of HCC

Steroid and MMF probably has limited effect on HCC recurrence or progression compared to the CNI and mTOR inhibitors, as previously mentioned. High concentration of cyclosporine in the first year after LT has been shown to increase HCC recurrence as compared to patients using low concentration. The same relationship has been demonstrated with tacrolimus as well (1). Although there are little evidence that MMF directly inhibits HCC, addition of MMF enables reduction of CNI and thus may indirectly reduce the possibility of HCC recurrence. mTOR, on the other hand,

is known to directly suppress tumor behavior of HCC and sirolimus-based immunosuppression has been shown to increase patient survival compared to conventional immunosuppression protocol using CNI in LT patients with HCC (2). Even in patients above Milan criteria, it has been demonstrated to increase recurrence free survival and overall patient survival (3). Although there are increasing clinical evidence of the positive effect of sirolimus HCC patients, all the studies to date were retrospective studies and we need more sound clinical data to draw a firm conclusion.

Immunosuppression after HCC Recurrence

Most HCC following LT recur within 3 years and the clinical environment such as recurrence within 12 months, bone metastasis and possibility of radical surgical treatment is the most important prognostic factors influencing patient survival. There has been no studies until now showing the effect of different immunosuppression on tumor progression but because of evidences favoring mTOR inhibitors, many authors recommend a sirolimus-based immunosuppression in high risk or recurred patients (4). Moreover, the inhibitory pathway of sorafenib, a novel antineoplastic drug used in advance HCC, is different from that of sirolimus, and when used together may provide re-

duction of tumor growth even in various phenotypically different HCC (5).

References

1. Vivarelli M, Cucchetti A, La Barba G, Ravaioli M, Del Gaudio M, Lauro A, et al. Liver transplantation for hepatocellular carcinoma under calcineurin inhibitors: reassessment of risk factors for tumor recurrence. *Ann Surg* 2008;248:857-62.
2. Toso C, Merani S, Bigam DL, Shapiro AM, Kneteman NM. Sirolimus-based immunosuppression is associated with increased survival after liver transplantation for hepatocellular carcinoma. *Hepatology* 2010;51:1237-43.
3. Kneteman NM, Oberholzer J, Al Saghier M, Meeberg GA, Blitz M, Ma MM, et al. Sirolimus-based immunosuppression for liver transplantation in the presence of extended criteria for hepatocellular carcinoma. *Liver Transpl* 2004;10:1301-11.
4. Majno P, Giostra E, Mentha G. Is there a customised immunosuppressive regimen for patients transplanted with hepatocellular carcinoma? *J Hepatol* 2005;43: 577-84.
5. Bhoori S, Toffanin S, Sposito C, Germini A, Pellegrinelli A, Lampis A, et al. Personalized molecular targeted therapy in advanced, recurrent hepatocellular carcinoma after liver transplantation: a proof of principle. *J Hepatol* 2010;52:771-5.