

Iodine-125 seed implantation and allogenic natural killer cell immunotherapy for hepatocellular carcinoma after liver transplantation: a case report

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Abstract: For advanced hepatocellular carcinoma (HCC) patients, liver transplantation (LT) is an optimal treatment with limitation of high risk of tumor recurrence related to the immunosuppressive chemotherapy as usually recommended. In this study, a 29-year-old man suffered from HCC recurrence after LT. He underwent radiotherapy (total dose: 45 Gy) but had no significant response. Then, he received iodine-125 seed implantation combined with allogenic natural killer (NK) cell immunotherapy. Liver function, immune function, circulating tumor cell counts and computed tomography scans were evaluated to determine the clinical effect. We found that this combined treatment produced enhanced immune function of the patient and reduction in tumor size. This is the first report of an efficacy and safety study about clinical regimen comprising allogenic NK cell immunotherapy combined with iodine-125 seed implantation for the treatment of HCC recurrence after LT.

Keywords: hepatic carcinoma, iodine seeds implantation, natural killer cells, allogenic

Introduction

Treatment of liver metastases after liver transplantation (LT) represents a clinical challenge. Most patients with hepatocellular carcinoma (HCC) are not completely free of the risk of tumor recurrence after LT. Currently, chemotherapy is the general therapeutic strategy; however, posttransplant immunosuppression following chemotherapy remains a major problem. Therefore, alternative therapies are urgently required for immunosuppressed HCC patients.

Implanting iodine-125 seeds into the tumor sites has been widely used for the treatment of liver cancer.¹ Iodine-125 releases 27.4–31.4 keV X-rays and 35.5 keV γ -rays, which kill tumor cells through free oxygen radical generation and ionization.² However, collateral damage to surrounding tissues and organs is reduced because iodine-125 is only effective over a 17 mm radiation radius.³ Furthermore, iodine-125 seed implantation promotes anticancer immune responses, which activate CD3⁺ and CD4⁺ cells.⁴

Natural killer (NK) cells are one of the most efficient components of innate immunity and also participate in adaptive immunity.^{5,6} NK cells exert efficient antitumor activity and have been exploited for anticancer therapy using an adoptive immunotherapy approach.^{7–10} Moreover, it is advisable to select killer cell immunoglobulin-like receptor (KIR) and its ligand, human leukocyte antigen (HLA) class I molecules mismatched alloreactive blood donor.¹¹

Here, we report the case of a 29-year-old Hungarian man with HCC recurrence after LT. We assessed the clinical efficacy and safety of iodine-125 seed implantation combined with allogenic NK cell immunotherapy as a potential therapeutic strategy.

Case presentation

This clinical trial was approved by the ethics committee of Guangzhou Fuda Cancer Hospital. According to the Declaration of Helsinki, written informed consent was obtained from the patient for publication of this case report.

Here, we report the case of a 29-year-old Hungarian man who underwent LT following resection of a sizable hepatic tumor in November 2014. Recurrence occurred in February 2015. The patient accepted radiotherapy (total dose: 45 Gy) from June 2015 to August 2015; however, the clinical result was unsatisfactory and the patient opted for further treatment with iodine-125 seed implantation combined with allogenic NK immunotherapy.

Iodine-125 seed implantation

Iodine-125 seed implantation was performed by Dr L. Zhou and his assistants. Following local anesthesia with the patient in a supine position and electrocardiogram (ECG) monitoring, iodine-125 seed strands were prepared for transplantation according to the computed tomography (CT) findings. Ten seeds, each with an activity of 0.7 mCi and a half-life period of 60.1 days, were implanted at the tumor border at intervals of 0.5 cm. The number of seeds deployed was determined based on the tumor size (matching dose ~120 Gy, usually ≤ 20 particles).

Allogenic NK cell immunotherapy

For allogenic NK cell immunotherapy, the donor (the patient's kinsfolk) was selected based on genotyping mismatch between recipient patient peripheral blood KIRs and HLA class I molecules of allogenic donor.^{12–17} KIR and HLA class I molecule typing were performed on the peripheral blood from allogenic donors and the recipient using the TIANamp Blood DNA Kit (Tiangen Biotech Co., Ltd., Beijing, China) and KIR/HLA-Cw Genotyping Low Resolution Kit (PCR-SSP; Super Biotechnology Developing Co., Ltd., Tianjin, China). KIR/HLA-Cw mismatch was defined as absence of one or more HLA alleles known to be ligands for the inhibitory *KIR* typing, using previously published criteria.¹⁸

Highly activated NK (HANK) cell preparation

HANK cells were prepared under good manufacturing practice (GMP) conditions using clinical-grade reagents.

The human NK cell in vitro culture synergistic kit (HAHK Bioengineering Co., Ltd., Shenzhen, China) was used to co-stimulate expansion and activation of NK cells in the blood mononuclear cells (MNCs) according to the manufacturer's instructions.^{15–19} Briefly, ~50 mL peripheral blood from the donor (the patient's kinsfolk was informed) was collected. The blood was transferred to a 50 mL conical tube and centrifuged at 600×g for 15 minutes. The plasma in the supernatant was collected into a 50 mL conical tube. Equal volume of saline was added to blood cells in the bottom, and the cells were resuspended for lymphocyte separation. The plasma tube was transferred into 56°C water bath for 30 minutes, made to stand on the bench top till the tube temperature was <37°C and centrifuged at 400×g for 10 minutes; the supernatant was then transferred into a new 50 mL conical tube and stored at 4°C for further applications. The plasma tube stored at 4°C for >12 hours was centrifuged again, and only the supernatant was used. In all, 20 mL of human lymphocyte separation solution (Haoyang Biological Manufacture Co., Ltd., Tianjin, China) was transferred into two 50 mL conical tubes. Carefully equal volume of the blood cell suspension was laid onto the lymphocyte separation solution in two 50 mL conical tubes and centrifuged at 600×g for 15 minutes. The lymphocytes in the middle layer were transferred into a 50 mL conical tube and washed twice with saline. The total cell number was counted. NK cell culture media consist of 1 L X-Vivo 15 serum-free medium (Lonza, Walkersville, MD, USA), one tube HK-002 and self (5% for initial 200 mL medium and then reduce to 1%–2%). Tube HK-001 contains membrane chimeric active cellular factors. One tube of HK-001 is good for 4×10^7 lymphocyte initial culture. The HK-001 tubes needed were calculated according to the lymphocyte numbers. HK-001 was taken out of liquid nitrogen or –80°C freezer and immediately put into 37°C water bath for recovery. Then, it was centrifuged at 350×g for 5 minutes and the supernatant was deserted. The precipitate was washed twice with saline. The precipitate with ~3 mL NK cell culture medium was resuspended. Then, NK cells were cultured with following procedures. On day 1, 4×10^7 lymphocytes, 50 mL NK cell culture medium and 1 tube of recovered HK-001 in a T175 culture flask (Corning Incorporated, NY, USA) incubated at 37°C with 5% CO₂ were mixed. On day 3, ~30 mL of NK cell culture medium was added to the T175 flask. On day 5, ~60 mL of NK cell culture medium was added to the T175 flask and the cell concentration was adjusted to $\sim 1 \times 10^6$ /mL. On day 6, ~60 mL of the NK cell culture medium was added to the T175 flask and the cell concentration was adjusted to $\sim 1 \times 10^6$ /mL.

On day 7, ~50 mL of the NK cell culture medium (1%–2% plasma concentration) was added to the T175 flask. The cell number was counted. If the total cell number was $>6 \times 10^7$, a tube of recovered HK-001 was added; if the total cell number was $3\text{--}6 \times 10^7$, a tube of recovered HK-001 was added on the eighth day. The first sterility test was performed. On day 8, the total culture from the T175 flask was transferred to the 2 L cell culture bag (Haoyang Biological Manufacture Co., Ltd.). Approximately 200 mL of the NK cell culture medium was added to the cell culture bag. On days 9, 10 and 11, ~150 mL of the NK cell culture medium was added to the cell culture bag each day. On day 12, ~350 mL of the NK cell culture medium was added to the cell culture bag. The quality control tests were performed including cell viability, NK cell purity, endotoxin, activity (cytotoxicity) and sterility.^{16,17} On day 13, HANK cells were harvested. The total cell number (should be $\sim 1 \times 10^{10}$) was counted. The cultures were collected into 450 mL conical centrifuge tubes. Cells were precipitated and washed once with saline. The cell concentration was adjusted to $\sim 2 \times 10^7$ /mL with cell infusion solution (400 mL saline with 1% human serum albumin and 6 mL HK-003). Approximately $3\text{--}5 \times 10^9$ HANK cells were harvested into a blood transfusion bag each day for infusion at a concentration of $\sim 2 \times 10^7$ /mL. The release tests were performed on each bag of cells.

Therapeutic procedure

Iodine-125 seed implantation was carried out on June 2016, and the cultured HANK cells were infused intravenously from July 2016 to October 2016 (Table 1). Two courses of treatments were performed monthly. Each course with three infusions was delivered consecutively over 3 days. The patient received six courses of treatments (18 infusions) in the therapeutic process.

Table 1 Clinical details and therapeutic procedure

Time	Therapy
November 2014	LT
February 2015	Recurrence
June–August 2015	Radiotherapy
June 2016	Iodine-125 seed implantation
July–October 2016	Allogenic NK cell immunotherapy
June–October 2017	Subsequent visit

Notes: Peripheral blood samples were collected from the patient for HANK cell isolation after iodine-125 seed implantation. After 1 month, the cultured HANK cells were intravenously infused in six courses (18 times) from July 2016 to October 2016.

Abbreviations: LT, liver transplantation; NK, natural killer; HANK, highly activated natural killer.

Safety and curative effect evaluation

Adverse events

The most common adverse reactions were recorded that included local (pain and retroperitoneal erythema) and systemic (chills, fatigue and fever) reactions.

Liver function

Liver function was evaluated based on the levels of ALT, AST, GGT and ALP before and after immunotherapy.

Detection of lymphocyte subsets and tumor markers

Lymphocyte subsets were detected by flow cytometry (FACSCanto™ II; Becton Dickinson, San Jose, CA, USA). Peripheral blood (2 mL) was drawn to assess the lymphocyte subsets before and after the HANK cell infusion. The number of CD3⁺, CD3⁺CD8⁺, CD3⁺CD4⁺, CD3⁺CD16⁺CD56⁺ and CD45⁺ cells was detected. The level of carbohydrate antigen 19-9 (CA19-9, reference range <39 U/mL) expression was determined by radioimmunoassay (Maglumi 2000 Plus) before and after the HANK cell infusion.

Circulating tumor cells (CTCs) were measured as a biomarker for identification of patients at high risk of relapse and to monitor immune responses to therapy.^{20,21} According to a previously published report, cells that were CD45 negative, CK positive and CD326 positive were defined as CTCs.¹⁰ In normal conditions, the reference number of CTCs is 0–1 cells/7.5 mL blood. CTCs ≥ 5 indicate poor prognosis and high risk of recurrence or metastasis. CTCs < 5 indicate low risk of recurrence or metastasis. The detection procedure includes collect 7.5 mL blood from the patient and isolate MNCs using human peripheral blood lymphocyte separation solution (Haoyang Biological Manufacture Co., Ltd.). Isolated cells were enriched by binding to magnetic CD326 (Ep-CAM) MicroBeads (Miltenyi Biotec Ltd., Bergisch Gladbach, Germany) using magnetic-activated cell sorting (MACS). Enriched cells were labeled with monoclonal antibodies targeting the epithelial cell antigens CD45, CD326 and cytokeratin 8, 18 and 19 (Miltenyi Biotec Ltd.) and counted by flow cytometry using a BD FACSCanto™ II apparatus (Becton Dickinson).

CT imaging change

The changes in CT tumor imaging were monitored to evaluate the curative effect of the treatment according to the evaluation standards published by the WHO.²² According to the degree of change in the largest transverse diameter, the therapeutic effect is categorized as a complete response (CR), disappearance of the arterial enhancement imaging of all target lesions; partial

Table 2 The result of genotyping of both host and donor

	Donor (patient's kinsfolk)	Recipient (patient)
Genotype	KIR2DL1, KIR2DL3, KIR2DS2	HLA-Cw3, HLA-Cw12

Note: According to a previously published report, we found KIR/HLA-Cw mismatch between donor and the patient.

response (PR), total reduction in the diameter of the target lesions >30%; stable disease (SD), tumor regression fails to reach PR or tumor progression fails to reach progressive disease (PD) and PD, total progression of the tumor diameter >20%. To accurately observe the therapeutic effects, the total area of all tumors before and after treatment was compared. The recent curative effect must be maintained for >4 weeks, with CR+PR representing the effective rate (RR).

Results

Genotyping of host and donor

Following genotyping test, we found KIR/HLA-Cw mismatch between donor and the patient according to previously published report.²³ The result is given in Table 2.

Identification of HANK cells

Before NK cell expansion, the median percentage of the CD3⁻ CD56⁺ population was 9.2% (range: 7.2%–13.3%). Following expansion, the proportion of viable cells exceeded 92% without any bacterial, fungal or mycoplasma contamination (endotoxin level <1 EU). The median proportion of CD56⁺ CD3⁻ cells was 86.3% (range: 80.1%–94.8%). The representative results are presented in Figure 1.

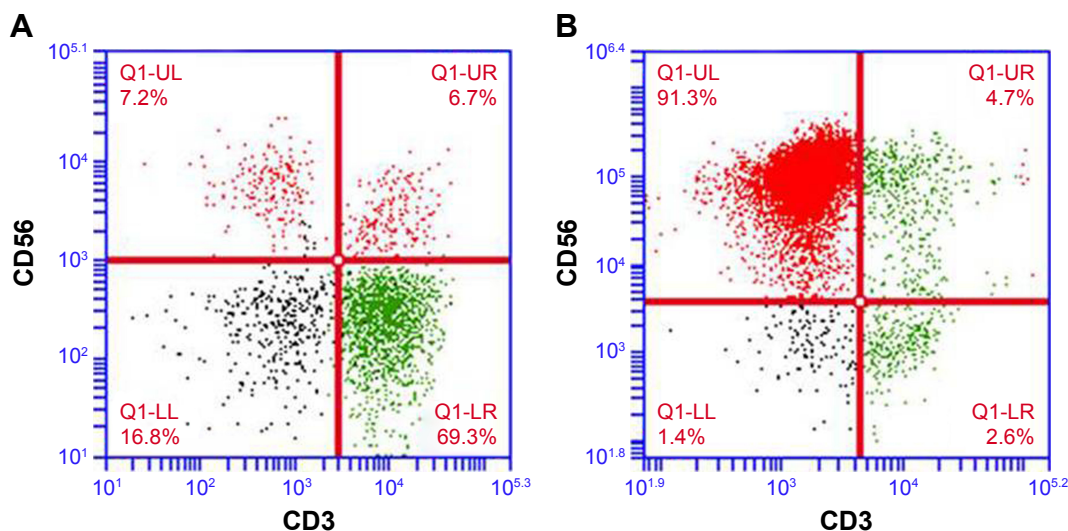


Figure 1 Proportion analysis of CD3⁻ CD56⁺ cells (NK cells).

Notes: (A) The proportion of NK cells before the expansion. (B) The proportion of NK cells after the expansion on Day 9.

Abbreviation: NK, natural killer.

Evaluation of safety and curative effect

During the HANK cell infusion, the patient did not report experiencing cold chills, fever or any other discomforts. After the treatment, the ALT, AST and GGT levels were reduced compared with the levels detected before treatment, while there was no effect on the ALP levels (Figure 2). The lymphocyte subsets of the patient were improved following allogeneic NK immunotherapy (Figure 3). The CA19-9 level increased after HANK cell infusion (Figure 4) but returned to normal numbers after a year, and CTCs also fell back to normal and were even stable after a year (Table 3).

CT imaging changes

Before iodine-125 seed implantation, the metastatic tumor size was 2.2×1.9 cm (Figure 5A). The size decreased to 2.0×0.9 cm at 2 months after treatment and 1.7×1.2 cm after 5 months (Figure 5B and C, respectively). The metastatic tumor size remained stable for at least a year after treatment (Figure 5D). As previously described, the patient achieved a PR following treatment, with an overall survival time of >18 months.²²

Discussion

For the majority of patients with advanced HCC, the tumor is unresectable. Chemotherapy, radiotherapy and other palliative treatments are options for patients with metastatic disease.^{24,25} A randomized controlled study by Chen et al²⁶ showed that iodine-125 seed implantation therapy following liver resection significantly prolonged the time to recurrence and overall survival rates. Nag et al²⁷ observed high complete or partial remission rates for unresectable HCC following

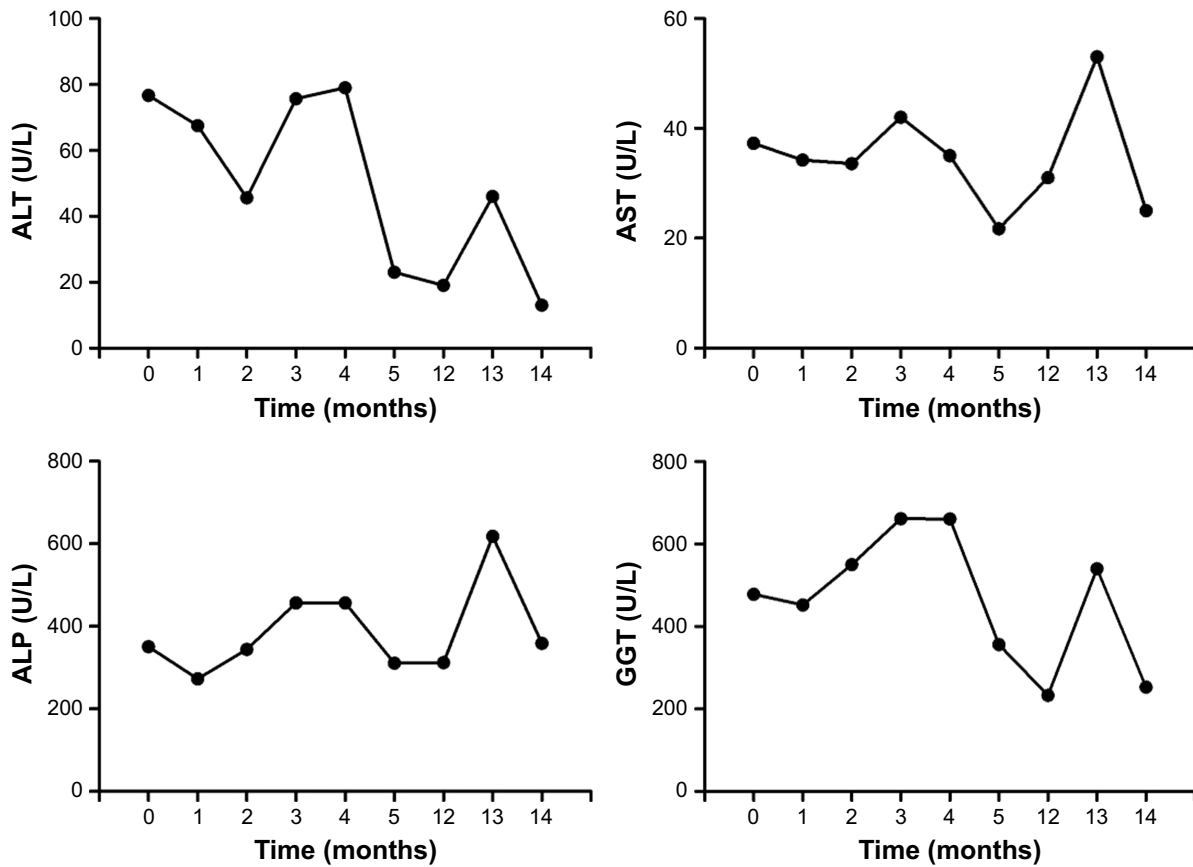


Figure 2 Liver function.
Note: The levels of ALT, AST and GGT were reduced except for ALP after treatment.

iodine-125 therapy. Furthermore, Chuan-Xing et al²⁸ reported that it was effective and safe to perform chemoembolization and implantation of stents with iodine-125 seeds for patients with HCC and portal vein thrombus. These studies indicated

the potential effectiveness of iodine-125 seed implantation in HCC recurrence therapy after LT. In addition, a prospective study by Chen et al²⁹ showed that radiofrequency ablation combined with percutaneous iodine-125 seed implantation (n=68) results in better 5-year survival rate (66.1% vs 47%, $P=0.003$) compared with the use of radiofrequency ablation

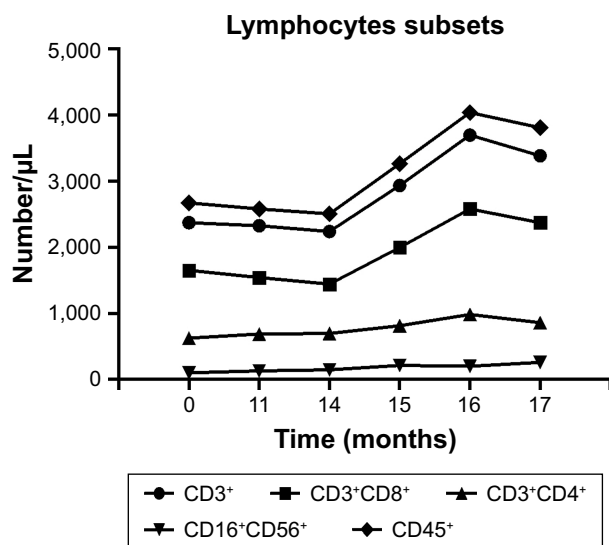


Figure 3 Detection of lymphocyte subsets.
Note: The lymphocyte subsets were gradually increased after iodine-125 seed implantation combined with allogenic HANK cell immunotherapy.
Abbreviation: HANK, highly activated natural killer.

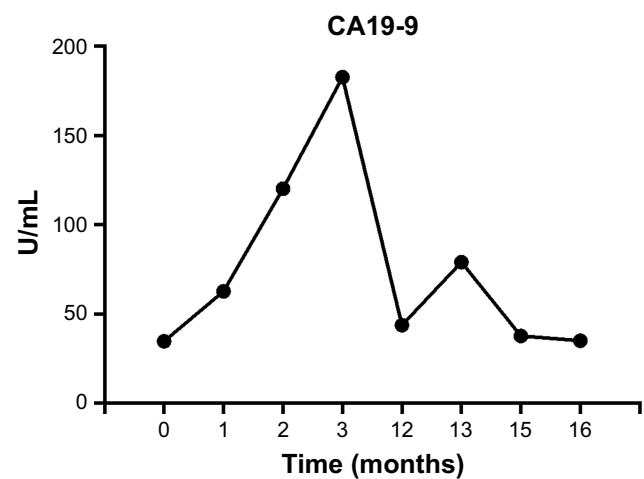


Figure 4 Tumor markers.
Note: CA19-9 levels increased following iodine-125 seed implantation combined with allogenic NK immunotherapy and reduced to the normal level after a year.
Abbreviation: NK, natural killer.

Table 3 The variation of CTCs numbers

Date	CTCs
July 21, 2016	3
August 17, 2016	19
August 26, 2016	0
August 25, 2017	0
October 27, 2017	2
December 1, 2017	0

Notes: CTCs fall back from high values (19 cell number/7.5 mL blood) to normal level (0–1 cell number/7.5 mL blood) following treatment and were even stable after a year. Reference: 0–1 cell/7.5 mL blood.

Abbreviation: CTCs, circulating tumor cells.

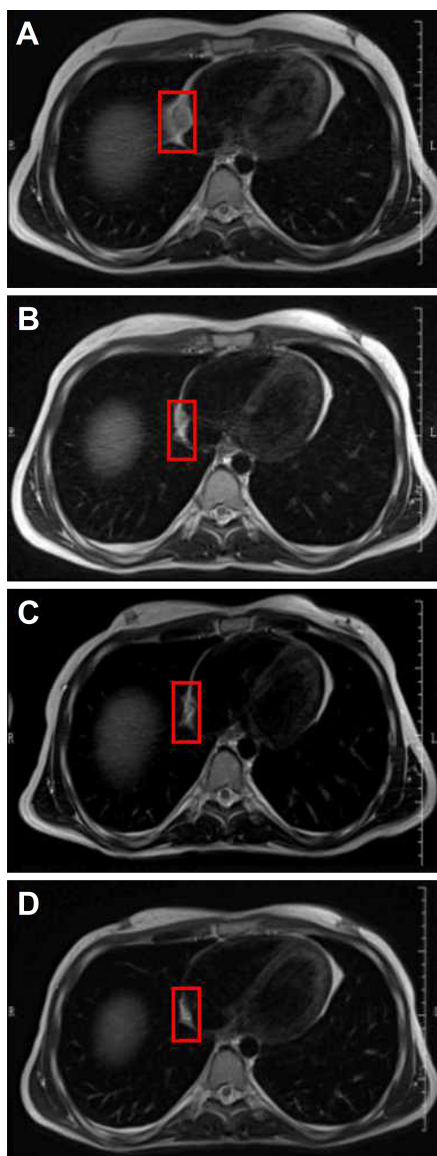


Figure 5 MRI of the patient before and after treatment.

Notes: (A) Lesion before treatment (June 2016): metastatic tumor size 2.2×1.9 cm (red rectangle). (B) Clinical effect at 2 months after iodine-125 seed implantation: metastatic tumor size 2.0×0.9 cm (red rectangle). (C) Clinical effect at 5 months after infusions of allogenic NK cells: metastatic tumor size 1.7×1.2 cm (red rectangle). (D) Regular follow-up visited at October 2017: metastatic tumor size 1.8×0.9 cm (red rectangle).

Abbreviations: MRI, magnetic resonance imaging; NK, natural killer.

alone (n=68) in patients with HCC. A case report from Xiong et al also showed that the liver function test was mildly abnormal except for a slight elevation in AST (65 IU/L) and ALT (60 IU/L) after iodine-125 seed implantation in a 48-year-old male patient with primary HCC and pancreatic metastasis. Moreover, the tumor size of the hepatic and metastasis was largely reduced after 15 months follow-up.³⁰ Although there is lack of clinical evidence in the tumor reduction in a specific time range, image-guided iodine-125 seed implantation has been regarded as an promising therapeutic approach to unresectable HCC.

In this study, we used the human HANK cell in vitro preparation kit to induce the expansion and activation of KIR-mismatched HANK cells. The patient received transfusions of 1×10^{10} HANK cells in each course of treatment. Our clinical data show that allogenic HANK cell immunotherapy achieved a partial clinical response and improved the quality of life of the patient, with no sign of graft vs host reaction (GVHR) or any other local or systemic side effects.

In HCC recurrence therapy after LT, NK cells play at least three important roles. The first role is to directly kill tumor cells. As part of the immune system, NK cells can destroy tumor cells and target cells without antigens or sensitization. NK cells can recognize and lyse cells lacking major histocompatibility complex (MHC) molecules via their activating receptors. Taking advantage of alloreactivity by the “missing-self” concept, a mass of studies has shown that infusion of haploidentical NK cells to exploit KIR/HLA alloactivity is safe and allogenic NK cell immunotherapy can obtain a better clinical effect than current approaches. The second role is immunoregulation function, which is very important for transplanted organ survival without immunosuppressive chemotherapy as reported for stem cell transplantation.^{31,32} The third role is the antiviral infection function of the NK cells, which is also crucial to prevent opportunistic viral infections and successful transplantation.^{33–38}

In conclusion, we report a case of partial clinical response to allogenic NK cell immunotherapy combined with iodine-125 seed implantation in an HCC patient after LT. Our findings provide evidence of the potential therapeutic safety and effectiveness of this regimen, which warrants further investigation in prospective clinical studies.

Disclosure

The authors report no conflicts of interest in this work.

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