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Robo1-specific CAR-NK Immunotherapy Enhances Efficacy of ^{125}I Seed Brachytherapy in an Orthotopic Mouse Model of Human Pancreatic Carcinoma

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Abstract. *Background/Aim: The aim of the current study was to investigate the synergistic efficacy of Robo1 bichimeric antigen receptor-natural killer cell (BiCAR-NK) immunotherapy and ^{125}I seed brachytherapy in an orthotopic pancreatic cancer mouse model. Materials and Methods: The orthotopic pancreatic tumor model was established with human pancreatic cancer BxPC-3 cells expressing red fluorescent protein. The mice were treated with ^{125}I seed implantation alone or the combination of ^{125}I seeds with Robo1-specific CAR-NK cells. To assess tumor inhibition, in vivo fluorescence imaging was conducted. 7 Tesla magnetic resonance (7T-MR) scanning was applied to measure the changes in the metabolic profiles of tumor tissues. Results: Tumor size was significantly reduced in the ^{125}I and ^{125}I +CAR-NK treated group compared to the untreated group ($p<0.05$). The ^{125}I seed +CAR-NK treated group showed significantly higher tumor reduction than ^{125}I seed treatment alone ($p<0.05$). T1 diffusion weighted imaging (T1DWI) sequence showed that the tumors of the ^{125}I +BiCAR-NK treated group had a significantly higher grey scale value than the tumors from the untreated control and the group treated with ^{125}I seed alone ($p<0.05$). Conclusion: Robo1 specific CAR-NK immunotherapy enhances efficacy of ^{125}I seed brachytherapy in an orthotopic pancreatic cancer mouse model.*

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Pancreatic cancer is one of the most aggressive and lethal human cancers with early local invasion and distant metastasis (1, 2). Despite advances in diagnosis and treatment, pancreatic cancer still has a very low 5-year survival rate (3).

Iodine 125 brachytherapy (^{125}I IBT) has recently been used alone or in combination with other treatments to treat patients with cancer at an inoperable advanced stage, or with local recurrence or metastasis following surgery, chemotherapy or radiotherapy (4, 5). It has been reported that ^{125}I IBT significantly inhibited local invasion and prolonged overall survival by maximizing the radiation dose delivered to the tumor and minimizing radiation injury of the surrounding normal tissue (6).

Recently, chimeric antigen receptor (CAR)-modified T cell therapy has emerged as a promising immunotherapeutic strategy for the treatment of blood cancers and some solid tumors (7, 8). Unlike T cells that require prior sensitization, NK cells can kill tumor cells directly (9). NK cells are activated by the integration of both stimulatory and inhibitory receptor signaling (10, 11). Similar to CAR-T cells, CAR-NK cell preparation includes collection of patient's NK cells, engineering of these cells to express CAR to recognize a tumor-specific protein, and then re-infusion of the engineered NK cells into the patient (12).

Robo1 is a member of the axon guidance receptor family (Robo1-4) (13) that has also been reported to play a role in modulating chemotaxis of T cells and tumor angiogenesis (14-16). Increased expression of Robo1 has been found in pancreatic cancer (17).

In this study, we examined the synergistic efficacy of Robo1 BiCAR-NK immunotherapy and ^{125}I seed brachytherapy in an orthotopic pancreatic tumor mouse model. To assess the inhibitory effect on tumor growth, *in vivo* fluorescence imaging was applied. 7T-MR scanning with 1H NMR spectra was used to determine the changes in the metabolic profiles of tumor tissues after ^{125}I seed and Robo1 CAR-NK combined therapy.

Materials and Methods

Cell culture. The human pancreatic cancer cell line BxPC-3 RFP was obtained from AntiCancer, Inc., (San Diego, CA, USA). The cells were cultured in RPMI 1640 (GIBCO Life Technologies, New York, NY, USA) modified medium containing 10% fetal bovine serum (FBS, Hyclone, Logan, UT, USA), L-Glutamine (2.05 mM), 100 U/ml penicillin and 100 μg/ml streptomycin at 37°C in 5% CO2 humidity saturated atmosphere.

Animal care. Male BALB/C nude mice, 18-20 g each, were purchased from Nanjing Biomedical Research Institute of Nanjing University (Nanjing, PR China) and were maintained in a HEPA-filtered environment at a standard condition. Animal experiments were approved by the Animal Use Committee of Nanjing Origin Biosciences, PR China.

Orthotopic mice model of human pancreatic cancer. Nude mice were subcutaneously injected with 5×10^6 BxPC-3-RFP cells. The tumor was harvested during the exponential growth phase for subsequent orthotopic tumor implantation. Viable tumor tissues with strong RFP expression were cut into 2-mm^3 fragments. Animals were anesthetized with a cocktail of ketamine, xylazine, and acepromazine maleate. An incision was made through the left upper abdominal pararectal line and peritoneum. The pancreas was exposed. Then, one tumor fragment was transplanted to the pancreatic tail with 8-0 surgical sutures. The abdomen was closed with sterile 5-0 surgical sutures.

Treatment. When the mean tumor volume reached 300 mm^3, the experimental animals were divided into three groups with 8 mice in each group. Group 1 was untreated and served as a normal control. The G2 group was treated with implantation of ^{125}I seeds in the tumor. The G3 group was treated with ^{125}I seeds in the tumor and injection of Robo1-specific BiCAR-NK cells. ^{125}I seeds (diameter, 0.8 mm; length, 4.5 mm; half life, 59.6 days; half value thickness, 1.7 cm in tissue; main emission, 27.4 31.4 Kev X ray and 35.5 Kev γ ray) were provided by Shanghai Xinke Pharmaceutical Co., Ltd. (Shanghai, PR China). The ^{125}I seeds were preloaded into 18 gauge needles and subsequently implanted into the xenograft center. A total of 10×10^8, 30×10^8 and 50×10^8 Robo1 CAR-NK cells were intravenously administered at day 1, 8 and 15, respectively, after ^{125}I seed treatment.

Fluorescence imaging. Tumor growth was monitored and measured by *in vivo* fluorescence imaging with a fluorescence stereo microscope model MZ650 (Nanjing Optic Instrument Inc., PR China) equipped with D510 long-pass and HQ600/50 band-pass emission filters (Chroma Technology, Brattleboro, VT, USA). Images were processed and analyzed with the use of IMAGE PRO PLUS 6.0 software (Media Cybernetics, Silver Spring, MD, USA). Tumor volume was determined with the formula $(L\times W^2)/2$, where W indicates the perpendicular minor dimension whereas L represents the major one. All mice were sacrificed at the end of the study. The tumor was removed from mice and weighed at autopsy.

In vivo magnetic resonance (MR) imaging. MR images were acquired using a 7Tscanner (Bruker, Billerica, MA, USA). The mice were anesthetized with 2% isoflurane in 100% oxygen. Anatomical proton MR images were acquired using the rapid acquisition with relaxation enhancement (RARE) sequence. T1-weighted images (T1WI) were acquired with the following parameters: repetition time (TR), 1300 msec; echo time (TE), 7.5 msec; slice thickness (ST), 1 mm; RARE factor, 4; number of acquisitions (NA), 2; matrix size, 256 Å~ 192; and field of view (FOV), 3.5Å~ 2.5 cm. The mice were imaged on days 7, 9, 11 and 13 after initial treatment. 7T-MR scanning was analyzed to measure the grey scale values in a region of interest (0.12 mm^2-0.20 mm^2) in the center of the tumor using Image J software.

Statistical analysis. Data are expressed as means±SD. SPSS 17.0 software (Chicago, IL, USA) was used to analyze the data. Differences between the groups were assessed using a one-way ANOVA. $p<0.05$ was considered to be statistically significant.

Results

Effect of ^{125}I seed and Robo1 BiCAR-NK combined therapy on the growth of the orthotopic pancreatic cancer BxPC-3-RFP. During the course of the treatment, tumor growth was monitored and measured with whole-body fluorescence imaging (Figure 1A). As shown in Figure 1B, the ^{125}I and ^{125}I+CAR-NK treated groups showed markedly tumor-growth reduction compared to the untreated control group beginning on day 15 post treatment initiation. The tumor size was significantly reduced in the ^{125}I and ^{125}I+BiCAR-NK treated groups compared to the untreated control group ($p<0.05$) at the end. Furthermore, the ^{125}I+CAR-NK treated group showed significantly higher tumor reduction than the ^{125}I alone treated group ($p<0.05$).

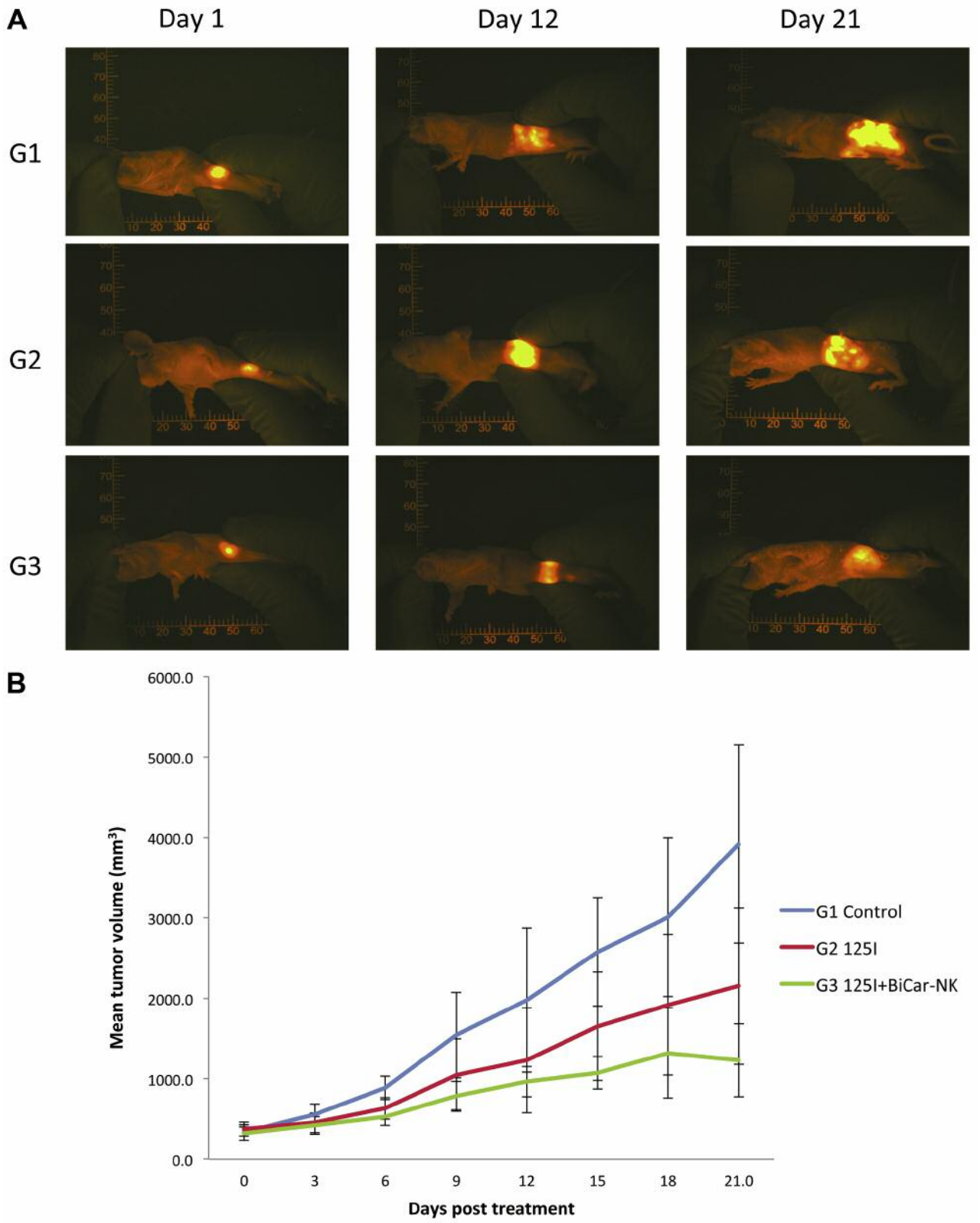

Figure 1. *Effect of ^{125}I seed and Robo1 CAR-NK combined therapy on the growth of the orthotopic pancreatic cancer BxPC-3-RFP. Tumor growth was monitored and quantified by real-time whole-body fluorescence imaging. (A) Sequential in vivo whole-body fluorescence imaging of tumors on days 1, 12 and 21 after initial treatment. (B) Tumor growth curves for each group.*

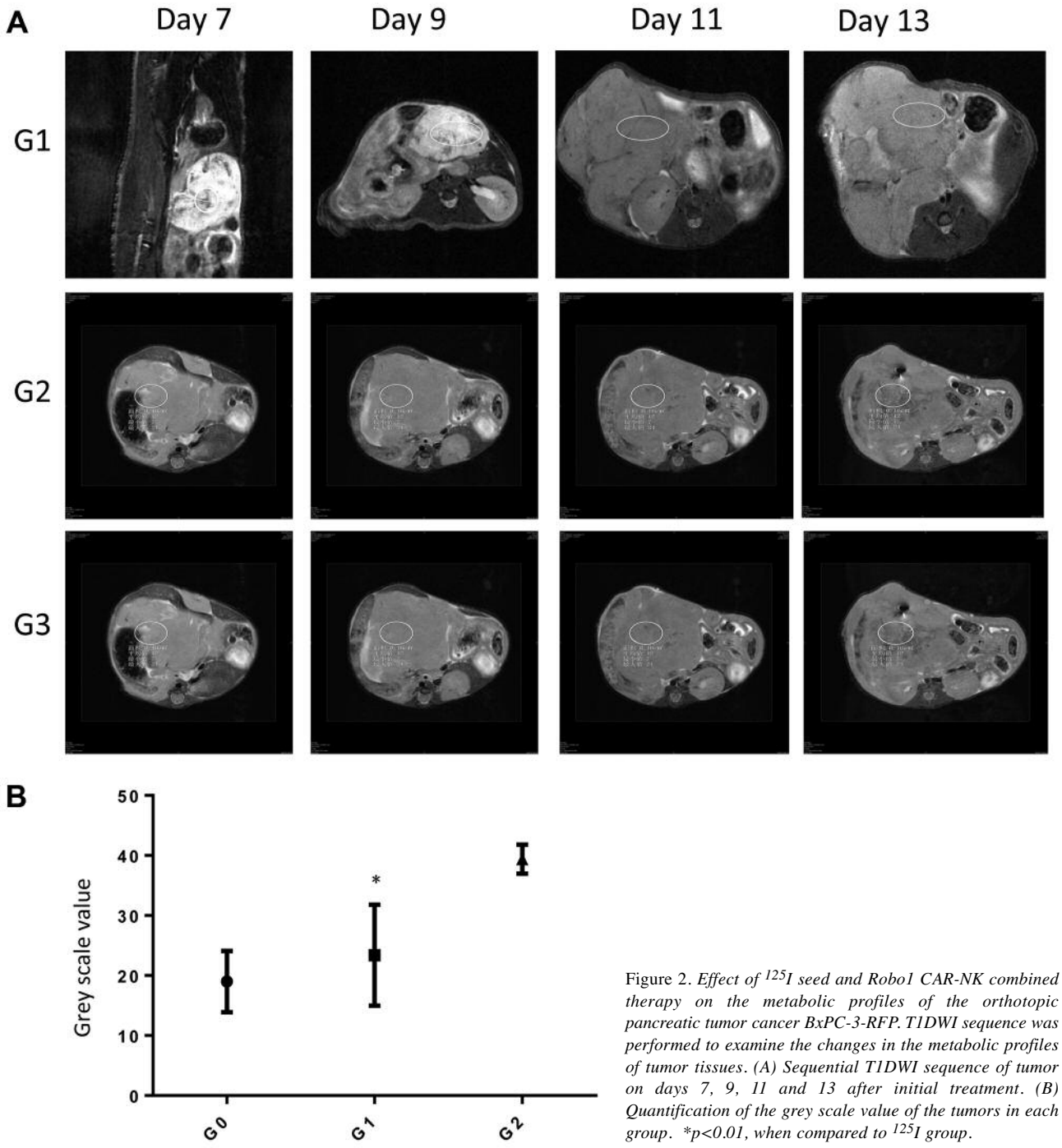

Figure 2. *Effect of ^{125}I seed and Robo1 CAR-NK combined therapy on the metabolic profiles of the orthotopic pancreatic tumor cancer BxPC-3-RFP. T1DWI sequence was performed to examine the changes in the metabolic profiles of tumor tissues. (A) Sequential T1DWI sequence of tumor on days 7, 9, 11 and 13 after initial treatment. (B) Quantification of the grey scale value of the tumors in each group. *$p<0.01$, when compared to ^{125}I group.*

Effect of ^{125}I seed and Robo1 BiCAR-NK combined therapy on the metabolic profiles of the orthotopic pancreatic cancer BxPC-3-RFP. T1-weighted images (T1WI) were acquired to evaluate the effect of ^{125}I seed and Robo1 BiCAR-NK combined therapy on orthotopic pancreatic cancer BxPC-3-RFP. T1DWI sequence showed that the tumors of the ^{125}I+CAR-NK treated group had significantly higher grey scale value than the tumors of the untreated control and ^{125}I seed-alone treated group ($p<0.05$) (Figure 2A and B), indicating that ^{125}I+CAR-NK treatment induced more necrosis in the tumor.

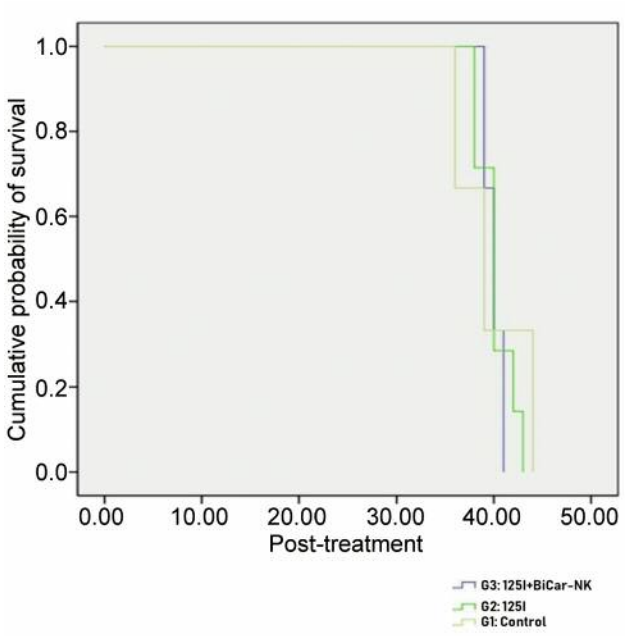

Figure 3. *Effect of ^{125}I seed and Robo1 CAR-NK combined therapy on the survival of nude mice with BxPC-3 pancreatic cancer. Overall survival of the animals in each group. No statistically significant difference in survival was found between the three groups (p>0.05).*

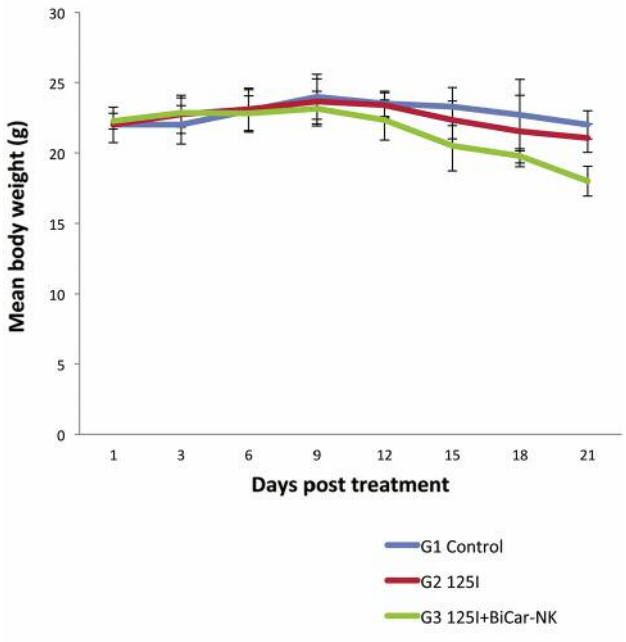

Figure 4. *Effect of ^{125}I seed and Robo1 CAR-NK combined therapy on the body weight of treated mice compared to untreated. No statistically significant difference for body weight loss was found among three groups (p>0.05).*

Effect of ^{125}I seed and Robo1 BiCAR-NK combined therapy on survival of tumor bearing mice. Control, ^{125}I seed alone and ^{125}I seed + CAR-NK treated groups had an overall survival of 42 (+1.223), 39 (+2.449) and 40 (+0.797) days, respectively. However, there was no statistically significant difference among the three groups (p>0.05) (Figure 3).

Body weight and toxicity. To evaluate the toxic side effects of the treatments, the body weight of mice was measured. A decrease in body weight was observed in all three groups beginning on day 15 after treatment (Figure 4). However, there was no statistically significant difference among the three groups (p>0.05). No physical or behavioral signs indicating adverse effects were observed in any treatment group.

Discussion

^{125}I brachytherapy is attracting more and more attention due to specific advantages. First, irradiation dose targeted to the tumor is applied in a single procedure. Second, irradiation outside the target tumor is reduced. Third, tumor killing continues over several weeks or months. Finally, percutaneous implantation is guided under ultrasound or CT (18, 19). ^{125}I brachytherapy has been used as a promising therapy for unresectable pancreatic cancers to maximize local dose and minimize irradiation of the surrounding normal tissue (20).

The clinical study of CAR-NK cell-based immunotherapy has been carried out for some types of cancer (21) including acute lymphoblastic leukemia (22), glioblastoma and neuroblastoma (23), breast cancer (24), multiple myeloma (25) and prostate cancer metastases (26). An advantage of NK cell-based immunotherapy is that functional, immortal NK cell lines are available for pre-clinical development compared to CAR-T cell-mediated immunotherapy. Among all NK cell lines, NK92 is the most promising cell line for clinical application. NK92-mediated immunotherapy is now tested in phase I/II clinical trials (27, 28). Similar to CAR-T cell-based immunotherapy, to specifically target different antigens, genetically modified NK cells use various CAR molecules (12, 29).

In the present study, we used Robo1 CAR-NK cells to investigate the synergistic efficacy of the combination of CAR-NK-Robo1 immunotherapy and ^{125}I seed brachytherapy for pancreatic cancer in an orthotopic nude mouse model. Robo1 BiCAR-NK is a CAR-modified NK92 cell line expressing an anti-human Robo1 antibody specifically targeting Robo1 on tumor cells. Our study showed that treatment with ^{125}I seed +CAR-NK resulted in significantly higher tumor reduction than treatment with ^{125}I seed alone, indicating that the combination of Robo1

BiCAR-NK therapy with ^{125}I seed brachytherapy is a promising strategy for the treatment of pancreatic cancer.

Conflicts of Interest

None of the Authors have any conflict of interest in regard to this study.

Authors' Contributions

Ning Xia, Zhongmin Wang and Fenju Liu designed the study. Ju Gong, Pang Haopeng, Yu Sun performed *in vivo* study. Jian Lu, Zhijin Chen, Yunfeng Zheng analyzed the data and prepared the figures. Ning Xia wrote the draft manuscript. Robert M. Hoffman and Zhijian Yang revised the manuscript.

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References

1 Kato K, Yamada S, Sugimoto H, Kanazumi N, Nomoto S, Takeda S, Kodera Y, Morita S and Nakao A: Prognostic factors for survival after extended pancreatectomy for pancreatic head cancer: influence of resection margin status on survival. Pancreas *38*: 605-612, 2009. PMID: 19629002. DOI: 10.1097/MPA.0b013e3181a4891d

2 Bilimoria KY, Talamonti MS, Tomlinson JS, Stewart AK, Winchester DP, Ko CY and Bentrem DJ: Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors: analysis of 3851 patients. Ann Surg *247*: 490-500, 2008. PMID: 18376195. DOI: 10.1097/SLA.0b013e31815b9cae

3 Siegel R, Ma J, Zou Z and Jemal A: Cancer statistics. CA Cancer J Clin *64*: 9-29, 2014. PMID: 24399786. DOI: 10.3322/caac.21208

4 Li W, Guan J, Yang L, Zheng X, Yu Y and Jiang J: Iodine 125 brachytherapy improved overall survival of patients with inoperable stage III/IV non small cell lung cancer versus the conventional radiotherapy. Med Oncol *32*: 395, 2015. PMID: 25428394. DOI: 10.1007/s12032-014-0395-8

5 Yu X, Li J, Zhong X and He J: Combination of Iodine 125 brachytherapy and chemotherapy for locally recurrent stage III non small cell lung cancer after concurrent chemoradiotherapy. BMC Cancer *15*: 656, 2015. PMID: 26445227. DOI: 10.1186/s12885-015-1657-3

6 Li W, Dan G, Jiang J, Zheng Y, Zheng X and Deng D: Repeated iodine 125 seed implantations combined with external beam radiotherapy for the treatment of locally recurrent or metastatic stage III/IV non small cell lung cancer: A retrospective study. Radiat Oncol *11*: 119, 2016. PMID: 27623620. DOI:10.1186/s13014-016-0688-5

7 Porter DL, Levine BL, Kalos M, Bagg A and June CH: Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. N Engl J Med *365*: 725-733, 2011. PMID: 30458878. DOI: 10.1186/s13045-018-0676-3

8 Kim MG, Kim D, Suh SK, Park Z, Choi MJ and Oh YK: Current status and regulatory perspective of chimeric antigen receptor modified T cell therapeutics. Arch Pharm Res *39*: 437-452, 2016. PMID: 26895243. DOI: 10.1007/s12272-016-0719-7

9 Robertson MJ, Cochran KJ, Cameron C, Le JM, Tantravahi R and Ritz J: Characterization of a cell line, NKL, derived from an aggressive human natural killer cell leukemia. Exp Hematol *24*: 406-415, 1996. PMID: 8599969.

10 Bakker AB, Wu J, Phillips JH and Lanier LL: NK cell activation: distinct stimulatory pathways counterbalancing inhibitory signals. Hum Immunol *61*: 18-27, 2000. PMID: 10658974. DOI: 10.1016/s0198-8859(99)00160-3

11 Long EO: Negative signaling by inhibitory receptors: the NK cell paradigm. Immunol Rev *224*: 70-84, 2008. PMID: 18759921. DOI: 10.1111/j.1600-065X.2008.00660.x

12 Glienke W, Esser R, Priesner C, Suerth JD, Schambach A, Wels WS, Grez M, Kloess S, Arseniev L and Koehl U: Advantages and applications of CAR-expressing natural killer cells. Front Pharmacol *6*: 21-27, 2015. PMID: 25729364. DOI: 10.3389/fphar.2015.00021

13 Legg JA, Herbert JM, Clissold P and Bicknell R: Slits and roundabouts in cancer, tumour angiogenesis and endothelial cell migration. Angiogenesis *11*: 13-21, 2008. PMID: 18264786. DOI: 10.1007/s10456-008-9100-x

14 Kidd T, Brose K, Mitchell KJ, Fetter RD, Tessier-Lavigne M, Goodman CS and Tear G: Roundabout controls axon crossing of the CNS midline and defines a novel subfamily of evolutionarily conserved guidance receptors. Cell *92*: 205-215, 1998. PMID: 9458045. DOI: 10.1016/s0092-8674(00)80915-0

15 Wang B, Xiao Y, Ding BB, Zhang N, Yuan Xb, Gui L, Qian KX, Duan S, Chen Z and Rao Y: Induction of tumor angiogenesis by Slit-Robo signaling and inhibition of cancer growth by blocking Robo activity. Cancer Cell *4*: 19-29, 2003. PMID: 12892710.

16 Prasad A, Qamri Z, Wu J and Ganju RK: Slit-2/Robo-1 modulates the CXCL12/CXCR4-induced chemotaxis of T cells. J Leukoc Biol *82*: 465-476, 2007. PMID: 17565045. DOI: 10.1189/jlb.1106678

17 He H, Di Y, Liang M, Yang F, Yao L, Hao S, Li J, Jiang Y, Jin C and Fu D: The microRNA-218 and ROBO-1 signaling axis correlates with the lymphatic metastasis of pancreatic cancer. Oncol Rep *30*: 651-658, 2013. PMID: 23733161. DOI: 10.3892/or.2013.2516

18 Wang J, Jiang Y, Li J, Tian S, Ran W and Xiu D: Intraoperative ultrasound-guided iodine-125 seed implantation for unresectable pancreatic carcinoma. J Exp Clin Cancer Res *28*: 88, 2009. PMID: 19545454. DOI: 10.1186/1756-9966-28-88

19 Zhongmin W, Yu L, Fenju L, Kemin C and Gang H: Clinical efficacy of CT-guided iodine-125 seed implantation therapy in patients with advanced pancreatic cancer. Eur Radiol *20*: 1786-1791, 2010. PMID: 20069424. DOI: 10.1007/s00330-009-1703-0

20 Montemaggi P, Dobelbower R, Crucitti F, Caracciolo F, Morganti AG, Smaniotto D, Luzi S and Cellini N: Interstitial brachytherapy for pancreatic cancer: report of seven cases treated with ^{125}I and a review of the literature. Int J Radiat Oncol Biol Phys *21*: 451-457, 1991. PMID: 2061121. DOI: 10.1016/0360-3016(91)90795-6

21 Rezvani K and Rouce RH: The application of natural killer cell immunotherapy for the treatment of cancer. Front Immunol *6*: 578, 2015. PMID: 26635792. DOI: 10.3389/fimmu.2015.00578
22 Chen KH, Wada M, Pinz KG, Liu H, Lin KW, Jares A, Firor AE, Shuai X, Salman H and Golightly M: Preclinical targeting of aggressive T cell malignancies using anti-CD5 chimeric antigen receptor. Leukemia *31(10)*: 2151-2160, 2017. PMID: 28074066. DOI: 10.1038/leu.2017.8
23 Esser R, Muller T, Stefes D, Kloess S, Seidel D, Gillies SD, Aperlo- Iffland C, Huston JS, Uherek C and Schonfeld K: NK cells engineered to express a GD2-specific antigen receptor display built-in ADCC-like activity against tumour cells of neuroectodermal origin. J Cell Mol Med *16*: 569-581, 2012. PMID: 21595822. DOI: 10.1111/j.1582-4934.2011.01343.x
24 Schonfeld K, Sahm C, Zhang C, Naundorf S, Brendel C, Odendahl M, Nowakowska P, Bonig H, Kohl U and Kloess S: Selective inhibition of tumor growth by clonal NK cells expressing an ErbB2/HER2-specific chimeric antigen receptor. Mol Ther *23*: 330-338, 2015. PMID: 25373520. DOI: 10.1038/mt.2014.219
25 Liu H, Pan Y, Meng S, Zhang W and Zhou F: Current treatment options of T cell-associated immunotherapy in multiple myeloma. Clin Exp Med *17*: 431-439, 2017. PMID: 28120217. DOI: 10.1007/s10238-017-0450-9
26 Topfer K, Cartellieri M, Michen S, Wiedemuth R, Muller N, Lindemann D, Bachmann M, Fussel M, Schackert G and Temme A: DAP12-based activating chimeric antigen receptor for NK cell tumor immunotherapy. J Immunol *194*: 3201-3212, 2015. PMID: 25740942. DOI: 10.4049/jimmunol.1400330
27 Arai S, Meagher R, Swearingen M, Myint H, Rich E, Martinson J and Klingemann H: Infusion of the allogeneic cell line NK-92 in patients with advanced renal cell cancer or melanoma: a phase I trial. Cytotherapy *10*: 625-632, 2008. PMID: 18836917. DOI: 10.1080/14653240802301872
28 Tonn T, Schwabe D, Klingemann HG, Becker S, Esser R, Koehl U, Suttorp M, Seifried E, Ottmann OG and Bug G: Treatment of patients with advanced cancer with the natural killer cell line NK-92. Cytotherapy *15*: 1563-1570, 2013. PMID: 24094496. DOI: 10.1016/j.jcyt.2013.06.017
29 Hermanson DL and Kaufman DS: Utilizing chimeric antigen receptors to direct natural killer cell activity. Front Immunol *6*: 195, 2015. PMID: 25972867. DOI: 10.3389/fimmu.2015.00195

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