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Original Article

Adjunctive immunotherapy enhances antitumor efficacy and improves survival of hepatocellular carcinoma patients

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Abstract: Adjunctive immunotherapy is an efficient treatment for cancers by stimulating cytotoxic lymphocytes activities against cancer cells. In this study, we determined whether the conventional cancer treatment combined with adjunctive immunotherapy could prolong the survival of patients with liver cancer. The retrospective cohort studies were studied in 320 newly diagnosed advanced hepatocellular carcinoma (HCC) patients from Jan 2011 to May 2015 in the national center for cancer treatment. Most of enrolled patients were undergone chemotherapy (25.6%), radiotherapy 88 (27.5%) or surgery (36.9%) for liver cancer treatments. The effects of adjuvant immunotherapy therapy were follow-up reports approximately maximal 4.33 years (for adjuvant immunotherapy users). The survival of patients with liver cancer treated by adjuvant immunotherapy were significantly extended associated with a decreased risk of metastasis and death compared with patients without immunotherapy therapy [hazard ratio (HR)=0.78, 95% confidence interval (CI)=0.74-0.92]. The protective effects against recurrence were enhanced and survival rate was improved significantly in liver cancer patients nursed by immunotherapy therapy. In conclusion, this respective cohort study suggests that adjunctive immunotherapy therapy improved the survival rate in patients with HCC and provided clinical information for further studies to confirm the potential role of adjunctive immunotherapy therapy in HCC.

Keywords: Adjunctive immunotherapy, hepatocellular carcinoma, long-term survival, respective cohort study

Introduction

Worldwide, hepatocellular carcinoma (HCC) is the second most common cause of cancer deaths and is the fifth (ninth) most common cancer in men (women) [1]. HCC is accounted for more than ninety percent of primary liver cancer cases [2]. Studies about HCC are a large-scale, multiregional andlongitudinal cohort [3, 4]. More and more reports are undertaken to study and improve treatment of patients with HCC, range from diagnosis to combined therapies [5]. There is increasing morbidity and mortality rate (746 000 deaths/782000 new cases) since from 2012, which making it only behinds in lung cancer in terms of cancer deaths [4]. The greatest economic burden of HCC affects more than 50% families in all cases in China [6, 7]. In addition, the overall prognosis and treatment of HCC patients remains poor despite more and more improvements in perioperative management, surgical techniques and other treatments [8]. Therefore, more effective therapeutic agents and combined treatments for HCC are urgently required for improving the high rate of occurrence and easier metastasis after curative resection in clinical [9].

Liver cancer presents poor prevention, treatment, prognosis and with only approximately 12% of 5-year overall survival rate [8]. Most of newly diagnosed liver cancer cases are often in advanced stage for lacking the sensitive screening diagnosis in early stage [10]. Traditional therapies including radiotherapy chemotherapy and surgery are limited to palliative approaches for advanced liver cancer [11]. However, many patients with HCC are poorly responded to these therapies or exposure limited outcomes [12]. Therefore, adjunctive therapeutic options are important for patients after received one or more anti-cancer medications.

Table 1. Characteristics of patients

	Number of Patients (n)	%
Patients with HCC	320	100
Gender		
Male	164	51.3
Female	156	48.7
Health volunteers	56	100
Gender		
Female	26	46.4
Male	30	53.6
ECOGPS		
0	173	54
1	147	46
Prior treatment		
Chemotherapy	82	25.6
Surgery	118	36.9
Radiotherapy	88	27.5
Other therapy	32	10.0
Drugs treatment		
Sensitized lymphocytes	244	29.8
Non-drug	76	39.8

The conventional therapies for human cancers are often ineffective and toxic for non-pathogenic sites except the poorly responded to cytotoxic chemotherapy therapies [13]. Cellular immunotherapy has immense potential to be a highly targeted alternative, which possesses the lowest or no toxicity to normal cells, in contrast high capacities to eradicate tumor [14-16]. Cellular immunotherapy often employs active immunization with immune cells including infiltrating T cells, efforts T cells and cytotoxic T cells that use adoptive transfer of T cells from patients themselves to directly target antigens on malignant cells [17, 18]. A large number of studies have proved these therapeutic approaches successful in human cancer therapy as adjunctive therapy [19-21]. In this study, we generated cellular therapies as adjunctive therapy by using active immunization with cancer cells from patients themselves. We examined adoptive transfer of effect or cells directly targeted HCC cells in liver cancer patients.

Nowadays, novel strategies medications for human liver cancer medical treatment have attracted popularity of clinicians and doctors [22, 23]. Adjunctive immunotherapy is very popular all over the world and plays an efficient role in modern healthcare system. The effects of adjunctive immunotherapy present targeting oncolytic outcomes bystimulating the host immune cells activated by homologous cancer cells. In this study, patients with liver cancer were designed to determine whether the combination of AIT with conventional cancer treatments prolong the survival of liver cancer patients. The cytotoxic activities of these immune cells can kill liver cancer by inducing apoptosis and inhibiting proliferation of tumor cells. Adjunctive immunotherapy also alleviated gene therapy-related and chemoradiotherapy-related side effects, even enhanced therapeutic effects of surgery and prolonged the survival of patient with liver cancer.

Materials and methods

Patients

320 patients with advanced HCC and 56 health volunteers were enrolled and treated with adjunctive immunotherapy therapy in clinical trials. All patients and health volunteers had written informed consent before enrolment in our clinical trials. The phase-I study (CH20118124) was conducted in Guide of Chinese clinical experiments between Jan 2011 to May 2015. All studies were conducted in accordance with European Medicines Agency requirements. Patients' age were ranged from 32 to 68 years and confirmed diagnosis of advanced HC by histological or clinical methods.

All patients with HCC received 10^8 sensitized lymphocytes intravenous injection every two days. Patients were managed until the occurrence of severe treatment-emergent adverse events. The treatment-emergent adverse events were defined by RECIST criteria [24]. The median overall survival was 4.33 years and was 2.4 years in non-sensitized lymphocytes group. The characteristic of patients were summarized in **Table 1** and Eastern Cooperative Oncology Group performance status was estimated from 0 to 1, < Grade 3 toxicity from immune therapy. The objective responses of patients were shown in **Table 4**.

Efficacy and safety assessments

Efficacy assessments contained the median percent reduction in patients with HCC and the

Table 2. Treatment-related adverse events of sensitized lymphocytes with an overall incidence ≥10%

	Total (n=54)	10^6-10^7 (n=22)	10^8-10^9 (n=23)	10^{10} (n=9)
Adverse event				
Proteinuria	18	4	7	7
Pain	11	3	4	4
Hypertension	20	7	8	5
Nausea	14	4	5	5
Vomiting	7	1	2	4
Lethargy	6	2	1	3
Rash	5	1	2	2
Fatigue	12	4	4	4
Decreased appetite	3	0	1	2
Weight decreased	3	1	1	1
Constipation	5	2	2	1
Hypertriglyceridemia	3	1	1	1
Epistaxis	1	0	0	1
Edema peripheral	3	0	1	2

Table 3. Treatment-related hypertension and proteinuria by Common Toxicity Criteria grade

	Total (n=54)	10^6-10^7 (n=22)	10^8-10^9 (n=23)	10^{10} (n=9)
Adverse event				
Hypertension	20	7	8	5
Grade 1	6	3	1	2
Grade 2	6	3	2	1
Grade 3	8	1	5	2
Proteinuria	18	4	7	7
Grade 1	7	2	2	3
Grade 2	7	2	3	2
Grade 3	4	0	2	2

responder rates of sensitized lymphocytes (10^7). A significant decreasing of median percent changes in cancer cell metastasis were observed in 60-day treatment period in sensitized lymphocytes group. The safety assessments contained the incidence rates of the most frequent treatment-emergent adverse events in 60-day treatment period in different groups. The safety analysis date included all patients received the drugs or not.

Cytokines analysis and anti-tumor activity

Plasma samples from patients with HCC were analyzed compared to baseline and levels of cytokines using anit-interleukin (IL)-2, IL-15, granulocyte-colony stimulating factor (G-CSF), and interferon (IFN)-γ antibody were analyzed after 60-day treatment with 10^7 dose of sensitized lymphocytes. The volume of tumor in patients was evaluated by nuclear magnetic resonance (3.0 T).

Statistical analysis

The data in this study were shown as means ± SD. Statistical significance of differences between mean values was assessed by Student's t test for unpaired data. Comparisons of data between multiple groups were performed with analysis of variance (ANOVA). $*P<0.05$, $**P<0.01$ was considered statistically significant.

Results

Patient characteristics

A total of one hundred and sixty patients were conducted clinical practice in this study between from May 2006 to June 2014 at Weifang City People's Hospital, Shandong, China. All patients exclude death received the study treatment and completed the full-course observation. Patients' age was ranged from forty-eight to sixty-nine years (average = fifty-five years old). In this study, all patients were from Asian and the numbers of men and women were roughly equal in the statistics. Most of these patients with HCC had undergone surgery, radiotherapy or/and chemotherapy (**Table 1**). Notably, almost 86% of patients had received at least one prior systemic therapy regimen, and about 27% of patients had received two systemic therapy regimens. In addition, about 15% of patients had received three regimens and 8% had received with four or more systemic therapy regimens. In addition, the Eastern Cooperative Oncology Group performance status (ECOGPS) was 0 in 54% patients and the remaining 46% patients was 1 in this study.

Duration of treatment, maximum tolerated and dose-limiting toxicities

The median overall duration of treatment of patients (n=54) with HCC was 10 days across all dosing cohorts of sensitized lymphocytes was 10^6, 10^7, 10^8, 10^9 and 10^{10}. In our results, the MTD dose cohort of the sensitized lymphocyte was identified 10^8 every two days. Dose-

Table 4. Treatment duration and response according to response evaluation criteria in HCC aftertreatment with sensitized lymphocytes (SLpys)

Dose level	No. of patients	Duration in months (range)	Best response, n (%)			
			Partial response	Stable disease	Progressive disease	Not evaluated
SLpys (10^6)	224	(0-52)	16 (7.1)	70 (31.3)	136 (60.7)	2 (0.9)
Non-drug	54	(0-50)	13 (24.1)	24 (44.4)	12 (22.2)	5 (9.3)
Total	278	(0-52)	29 (10.4)	94 (33.8)	148 (53.2)	7 (2.6)

limiting toxicities occurred in five (55.6%) patients after treatment with 10^8-sensitized lymphocytes. Dose-limiting toxicities occurred in two (28.6%) patients with condition of Grade 3 proteinuria and five patients (62.5%) with Grade 3hypertension in the 10^8-sensitized lymphocyte cohort (**Table 2**). Therefore, 10^7 sensitized lymphocytes were considered not tolerable for patients with HCC. Therefore, the dose was reduced to 10^7 and 10^7-sensitized lymphocytes were defined as MTD for patients with HCC. In addition, partial patients required to reduce adjunctive immunotherapy therapy for cumulative toxicity for a higher hypertension and proteinuria (**Table 3**). Therefore, most of patients were received a dose of 10^6 sensitized lymphocytes, whose was aim to further study the treatment of both the tolerability and antitumor effects.

Anti-tumor activity and safety

To investigate clinical design of sensitized lymphocytes for patients with HCC, therapeutic effects were observed in a 60-day period. One hundred and thirty-six patients (60.7%) improved progressive disease rate (PD) in a best response manner in our research. Clinical benefit (PD rate plus stable disease rate (SD rate) occurred in 92% patients (n=224) (**Table 4**).

In this study, 300 patients remained on treatment with adjunctive immunotherapy therapy. In **Figure 1A** showed that the volumes of tumors were decreased in all patients with liver cancer ranging from 26.0% to 78.3% compared to baseline. The results in **Figure 1B** demonstrated that immunotherapy therapy resulted in generation of tumor-specific CTL responses, which contributed to the long-term survival of patients. Also, the cytokines related immunostimulatory effects were tested, the levels of IL-2, IL-15, G-CSF, and IFN-γ increased significantly (***P*< 0.01) after the last dose of sensitized lymphocytes compared with baseline levels and non-sensitized lymphocytes patients (**Figure 1C**). Furthermore, all patients with HCC treated by immunotherapy therapy had a median progression-free survival (PFS) of 868 days (**Figure 1D**), which beyond the average survival time of liver cancer patients. Moreover, patients with HCC received at least one dose of study therapy with post baseline safety evaluation were included in the safety population. After the last sensitized lymphocyte dose. The most common treatment-related AEs were hypertension, pain, nauseavomiting, lethargy, rash and proteinuria (**Table 3**).

Discussion

The cytotoxicity of immune system for malignant cells plays an important role in human beings and animals cancer therapy [25, 26]. Failure of the immune cells to monitor and ignore tumor cells by decoyis the primmest motivator, which leads to the emergence and development of human cancers [27, 28]. Moreover, tumors cells escaping from immune-mediated cytotoxicity by using multiple ways have been elaborated in previous studies [29-31]. However, the most important of freedom from surveillance factors are depended on the lacking of recognition of tumor antigen.

This study was investigated the effects of immunotherapy on the survival rate and conditions of long-term survival in patients with HCC in large-scale cohorts. The therapeutic effects on patients' survival were evaluated by analysis of adjunctive immunotherapy and maximum tolerated and dose-limiting toxicities were performed in small-scale cohort of patients with liver cancer at Shandong province in China. 320 liver cancer patients and 56 health volunteers were enrolled in our retrospective cohorts study. The significant protective effects of adjunctive immunotherapy were observed with a 52.3% reduction on survival in control groups in long-term observation for all patients with HCC.

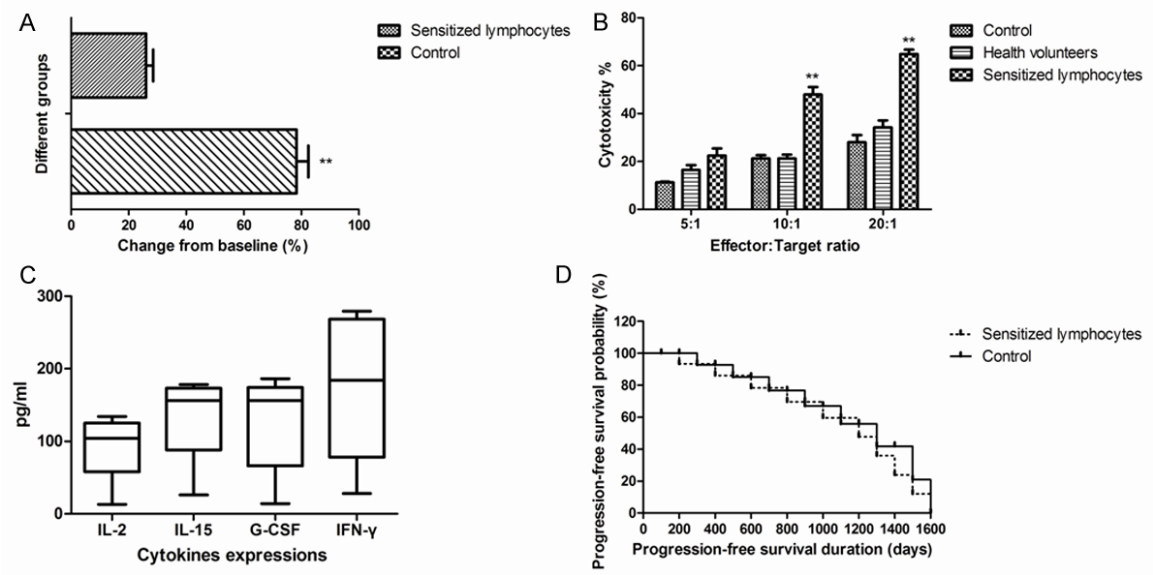

Figure 1. Therapeutic effects of sensitized lymphocytes and survival of patients with HCC. A. Tumor responses to sensitized lymphocytes (10^6) were displayed by waterfall plots. B. Sensitized lymphocytes enhanced immune responses by CTL response against liver cancer cellswith non-treated patients as control. C. Levels of cytokines for IL-2, IL-15, G-CSF and IFN-γ from predose baseline to Day 60 (measured every four days). D. Kaplan-Meier plots representing progression-free survival for patients with HCC. Measurements were recorded as per the Response Evaluation Criteria in HCC. Abbreviation: CI = confidence interval.

To date, previous reports have clearly understood that not only cellular immunity including T, NK cells can provide strong antitumor effects, but also evidenced that incurable cancers patients could be cured after received immunotherapy [32, 33]. In this study, peripheral blood from patients with HCC were extracted and lymphocytes were sensitized by tumor cells isolated from patients themselves, which improves clinical protocols and inhibits immune escape and tumor-induced immune suppression, as well as produces litter or without side effects. The prescriptions of intravenous injection for patients with liver cancer were similar to previous report [34]. No significant changes of body weight, anorexia and erythra were observed during the treatment period. However, the incidence of hypertension (48%) was relative higher than control patients with HCC. This may be the immunoreaction of the injected sensitized lymphocytes targeted for the purpose tumor cells. Immune responses have caused body's temperature in fervescence period, but returned to normal temperature within 24 hours.

Although, most of patients had received at least one prior systemic therapy regimen, there were 15% patients in adjunctive immunotherapy group and 52% patients in control group occurred metastatic. Immunologic functions of patients received adjunctive immunotherapy were significantly improved and blood coagulation was rarely occurred in patients treated by adjunctive immunotherapy. Tumor bearing living patients was accounted of 72% without affect the quality of life. In this study, we did not consider other diseases for there were no direct evidences indicated that adjunctive immunotherapy was associated with other diseases or side effects in patients with HCC.

Furthermore, we observed the increasing levels of IL-2, IL-15, G-CSF, and IFN-γ in group of adjunctive immunotherapy. Expressions of immune factors in plasma levels are biomarkers that are important mediators of cytotoxic T lymphocytes after immune-related anticancer treatments, which contribute to the mmunological memory for cancer patients [35, 36]. Changes in levels of various immune factors in blood in patients suggest that immune system has been enhanced by conducting of adjunctive immunotherapy at the indicated dose in our trials. We also demonstrated that antitumor activities were promoted after receiving adjunctive immunotherapy, which conducted significant protective effects on meta-

static tumor cells. Notably, tumor shrinkage was observed in most patients treated by immunotherapy. And there were 15 patients kept progression-free survival until the end of the observation period.

In conclusion, the beneficial effects of adjunctive immunotherapy on improvement of survival of patients with HCC were clinically observed after the primary treatments such as radiotherapy chemotherapy and surgery. Our data suggest that immunotherapy as adjunctive is significant and effective therapeutic schedule for patients with HCC and show that high expression levels of immune factors contribute to long-term survival of patients with HCC. The clinical relevance of more adjunctive immunotherapy for cancer patients needs further development in prospective larger-scale trails.

Disclosure of conflict of interest

None.

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References

[1] Uhry Z, Belot A, Colonna M, Bossard N, Rogel A, Iwaz J, Mitton N, Grosclaude P and Remontet L. National cancer incidence is estimated using the incidence/mortality ratio in countries with local incidence data: is this estimation correct? Cancer Epidemiol 2013; 37: 270-277.

[2] Capocaccia R, Buzzoni C, Grande E, Inghelmann R, Bellu F, Cassetti T, de Dottori M, Donato A, De Lisi V, Falcini F, Federico M, Ferretti S, Fusco M, Giacomin A, Guzzinati S, Mangone L, Piffer S, Rosso S, Sechi O, Tagliabue G, Tumino R, Vercelli M and Vitarelli S. Estimated and observed cancer incidence in Italy: a validation study. Tumori 2007; 93: 387-391.

[3] Lee JH, Lee Y, Lee M, Heo MK, Song JS, Kim KH, Lee H, Yi NJ, Lee KW, Suh KS, Bae YS and Kim YJ. A phase I/IIa study of adjuvant immunotherapy with tumour antigen-pulsed dendritic cells in patients with hepatocellular carcinoma. Br J Cancer 2015; 113: 1666-76.

[4] Lau CS, Mahendraraj K and Chamberlain RS. Hepatocellular Carcinoma in the Pediatric Population: A Population Based Clinical Outcomes Study Involving 257 Patients from the Surveillance, Epidemiology, and End Result (SEER) Database (1973-2011). HPB Surg 2015; 2015: 670728.

[5] Cucchetti A, Sposito C, Pinna AD, Citterio D, Ercolani G, Flores M, Cescon M and Mazzaferro V. Effect of age on survival in patients undergoing resection of hepatocellular carcinoma. Br J Surg 2015; 103: e93-9.

[6] Xiao J, Huang JP, Zhang M, Zhu JY, Wu GY and Gao YX. [Trends and forecast of hepatocellular carcinoma in Nantong, China: mortality rates from 1999 to 2011]. Zhonghua Gan Zang Bing Za Zhi 2015; 23: 663-668.

[7] Chen DS, Liaw YF, Chen CJ, Wu JC, Chuang WL, Peng CY and Chien RN. Differences in hepatitis viral etiology of hepatocellular carcinoma in Taiwan and China. Hepatology 2016; 64: 1008-9.

[8] Tsochatzis EA, Meyer T and Burroughs AK. Hepatocellular carcinoma. N Engl J Med 2012; 366: 92; author reply 92-93.

[9] Sherman M. Recurrence of hepatocellular carcinoma. N Engl J Med 2008; 359: 2045-2047.

[10] Asrani SK, Warnes CA and Kamath PS. Hepatocellular carcinoma after the Fontan procedure. N Engl J Med 2013; 368: 1756-1757.

[11] El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011; 365: 1118-1127.

[12] Wands JR. Prevention of hepatocellular carcinoma. N Engl J Med 2004; 351: 1567-1570.

[13] Hui D, Elsayem A, Li Z, De La Cruz M, Palmer JL and Bruera E. Antineoplastic therapy use in patients with advanced cancer admitted to an acute palliative care unit at a comprehensive cancer center: a simultaneous care model. Cancer 2010; 116: 2036-2043.

[14] Lage A. Immunotherapy and complexity: overcoming barriers to control of advanced cancer. MEDICC Rev 2014; 16: 65-72.

[15] Massarelli E, Papadimitrakopoulou V, Welsh J, Tang C and Tsao AS. Immunotherapy in lung cancer. Transl Lung Cancer Res 2014; 3: 53-63.

[16] Yamamoto N, Suyama H, Yamamoto N and Ushijima N. Immunotherapy of metastatic breast cancer patients with vitamin D-binding protein-derived macrophage activating factor (GcMAF). Int J Cancer 2014; 135: 1509.

[17] Matsuda G, Imadome K, Kawano F, Mochizuki M, Ochiai N, Morio T, Shimizu N and Fujiwara S. Cellular immunotherapy with ex vivo expanded cord blood T cells in a humanized mouse model of EBV-associated lymphoproliferative disease. Immunotherapy 2015; 7: 335-341.

[18] Pan QZ, Tang Y, Wang QJ, Li YQ, Zhang L, Li XD, Zhao JJ, Weng DS, Liu Q, Huang LX, He J, Chen SP, Ke ML, Zeng YX and Xia JC. Adjuvant cellular immunotherapy in patients with resected primary non-small cell lung cancer. Oncoimmunology 2015; 4: e1038017.

[19] Mostafa AA and Morris DG. Immunotherapy for Lung Cancer: Has it Finally Arrived? Front Oncol 2014; 4: 288.
[20] Wen Y, Graybill WS, Previs RA, Hu W, Ivan C, Mangala LS, Zand B, Nick AM, Jennings NB, Dalton HJ, Sehgal V, Ram P, Lee JS, Vivas-Mejia PE, Coleman RL and Sood AK. Immunotherapy targeting folate receptor induces cell death associated with autophagy in ovarian cancer. Clin Cancer Res 2015; 21: 448-459.
[21] Wefers C, Lambert LJ, Torensma R and Hato SV. Cellular immunotherapy in ovarian cancer: Targeting the stem of recurrence. Gynecol Oncol 2015; 137: 335-342.
[22] Kwok WW. Modulation of Peanut-specific humoral and cellular responses pre- and post-oral immunotherapy. Clin Exp Allergy 2015; 45: 1146-1149.
[23] Siddiqi T and Rosen ST. Novel biologic agents for non-Hodgkin lymphoma and chronic lymphocytic leukemia-part 2: adoptive cellular immunotherapy, small-molecule inhibitors, and immunomodulation. Oncology (Williston Park) 2015; 29: 299-308.
[24] Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92: 205-216.
[25] Kobold S, Duewell P, Schnurr M, Subklewe M, Rothenfusser S and Endres S. Immunotherapy in Tumors. Dtsch Arztebl Int 2015; 112: 809-815.
[26] Senda M, Bessho K, Oshima E, Sakamoto S, Tanaka K, Tsutsui K, Kanbayashi T, Takaki M and Yoshimura B. Anti-Inflammatory Therapy and Immunotherapy Were Partially Effective in a Patient With Anti-N-Methyl-D-Aspartate Receptor Antibodies and a Special Subgroup of Treatment-Resistant Schizophrenia. J Clin Psychopharmacol 2016; 36: 92-3.
[27] Saoji V, Lade NR, Gadegone R and Bhat A. Immunotherapy using purified protein derivative in the treatment of warts: An open uncontrolled trial. Indian J Dermatol Venereol Leprol 2016; 82: 42-6.
[28] Dhami S, Nurmatov U, Halken S, Calderon MA, Muraro A, Roberts G, Du Toit G, Kleine-Tebbe J, Larenas-Linnemann D, Lau S, Matricardi PM, Pajno G, Papadopoulos NG, Pfaar O, Ryan D, Santos AF, Timmermanns F, Wahn U and Sheikh A. Allergen immunotherapy for the prevention of allergic disease: protocol for a systematic review. Pediatr Allergy Immunol 2016; 27: 236-41.
[29] Pawelec G. Immunotherapy and immunoselection-tumour escape as the final hurdle. FEBS Lett 2004; 567: 63-66.
[30] Chouaib S. Tumor escape from the immune response: a major hurdle for successful immunotherapy of cancer? Tunis Med 2005; 83 Suppl 12: 7-10.
[31] Plate JM and Fidler MJ. Immunotherapy to overcome lung tumor cell-induced escape from immunosurveillance. Immunotherapy 2010; 2: 757-760.
[32] Malmberg KJ. Effective immunotherapy against cancer: a question of overcoming immune suppression and immune escape? Cancer Immunol Immunother 2004; 53: 879-892.
[33] Tjin EP, Krebbers G, Meijlink KJ, van de Kasteele W, Rosenberg EH, Sanders J, Nederlof PM, van de Wiel BA, Haanen JB, Melief CJ, Vyth-Dreese FA and Luiten RM. Immune-escape markers in relation to clinical outcome of advanced melanoma patients following immunotherapy. Cancer Immunol Res 2014; 2: 538-546.
[34] Sutoh M, Kasuya E, Yayou KI, Ohtani F and Kobayashi Y. Intravenous tryptophan administration attenuates cortisol secretion induced by intracerebroventricular injection of noradrenaline. Anim Sci J 2015; 87: 266-70.
[35] Sun L, Guo H, Jiang R, Lu L, Liu T and He X. Engineered cytotoxic T lymphocytes with AFP-specific TCR gene for adoptive immunotherapy in hepatocellular carcinoma. Tumour Biol 2016; 37: 799-806.
[36] Dong T. CD8+ cytotoxic T lymphocytes in human influenza virus infection. Natl Sci Rev 2015; 2: 264-265.