Int J Clin Exp Med 2016;9(7):13828-13835
www.ijcem.com /ISSN:1940-5901/IJCEM0024282

*Original Article*

# Clinical analysis of adoptive immunotherapy after autologous peripheral blood stem cell transplantation in B lymphocyte malignant lymphoma

Cun-Bang Wang*, Yao-Zhu Pan*, Rui Xi, Shu-Fen Xu, Qian Zhang, Yan Chen, Jin-Mao Zhou, Tao Wu, Hai Bai

*Department of Hematology, Lanzhou General Hospital, Chinese PLA, Lanzhou 730050, China. *Equal contributors.*

Received January 18, 2016; Accepted May 17, 2016; Epub July 15, 2016; Published July 30, 2016

**Abstract:** The purpose of this study was to investigate the efficacy of treatment with autologous peripheral blood stem cell transplantation (APBSCT) combined with adoptive immunotherapy in B lymphocyte malignant lymphoma (ML). According to receiving adoptive Immunotherapy or not after APBSCT, the patients were divided into two groups: treatment group and control group. 110 case patients [78 cases with non-Hodgkin's lymphoma (NHL), 32 cases with Hodgkin's lymphoma (HL)] from January 2000 to December 2009 were enrolled in a treatment group, while 74 cases (54 NHL, 22 HL) from January 1995 to December 1999 were taken as control. All of patients were treated sequentially with chemotherapy regimens for 6 courses. After that, all the patients received APBSCT. After hematopoietic reconstruction, the patients in treatment group were given six courses adoptive immunotherapy (rhIL-2 100 WU/day for 10 days monthly for each course) while the patients as control group were not given immunotherapy. All patients were followed-up for more than 5 years. The result showed that: 1. One patient in treatment group died for liver failure in three months, and one died for cerebral hemorrhage in two months; the other patients all achieved hematopoietic reconstruction. 2. Follow-up for 1, 3, 5 years, the disease free survival (DFS) rate in treatment group was 97.3%, 93.6% and 87.3%, respectively, while in control group was 91.9%, 73.0% and 64.9%, respectively. Follow-up for 3 and 5 years, there is significant difference in DFS between two groups (P<0.01). The DFS rate for 1, 3 and 5 year in treatment group of the patients in stage I/II and III/IV were 100%, 100%, 91.7% and 96.5%, 91.9%, 86.0%, respectively, while in control group was 100%, 93.3%, 86.7 and 89.8%, 67.8%, 59.3% respectively. There is significant difference of DFS for III/IV stage patients between two groups after following up for 3, 5 years (P<0.01). 3. The DFS rate for 1, 3 and 5 year in HL patients is 100%, 93.8% and 84.4% in treatment group, while that is 100%, 72.7% and 59.1% in control group, respectively. Follow-up for 3 and 5 years, there is significant difference of DFS in HL patients between two groups (P<0.05). The DFS rate for 1, 3 and 5 year in stage I/II HL patients is 100%, 100% and 88.9% in treatment group, while that is 100%, 100% and 80.0% in control group. The DFS for 1, 3 and 5 year in HL patients in stage III/IV is 100%, 91.3% and 82.6%, while that is 94.1%, 64.7% and 52.9% in control group, respectively. There is significant difference of DFS in III/IV stage patients between HL of two groups after following up for 3, 5 years (P<0.05). 4. The DFS rate for 1, 3 and 5 year in NHL patients is 96.2%, 93.6% and 88.5 in treatment group, while that is 90.4%, 73.1% and 65.4% in control group, respectively. Follow-up for 3 and 5 years, there is significant difference of DFS in NHL patients between two groups (P<0.01). The DFS rate for 1, 3 and 5 year in NHL patients in stage I/II is 100%, 100% and 93.3.9% in treatment group, while that is 100%, 90% and 90.0% in control group. The DFS for 1, 3 and 5 year in NHL patients in stage III/IV is 95.2%, 92.1% and 87.3%, while that is 88.1%, 69.0% and 59.5% in control group, respectively. There is significant difference of DFS in NHL patients in III/IV stage between two groups after following up for 3, 5 years (P<0.05). Conclusion: The results are satisfactory for patients with B lymphocyte ML and treating with adoptive immunotherapy after APBSCT, especially the patients in stage III/VI.

**Keywords:** Malignant lymphoma, B lymphocyte, autologous peripheral blood stem cell transplantation, adoptive immunotherapy, efficacy

## Introduction

Malignant lymphoma (ML) originated from human lymphoid hematopoietic system, with the clinical characteristics of lymphadenectasis involving all the organs [23]. The incidence of ML was exactly high, which was with 11rd to 13nd malignant tumor in China. In America,

**Table 1.** Clinical material of patient

| Group | Cases | Median age (years) | Sex (M/F) | Disease status in diagnosis | | | | KPS score | | IPI | | | | Symptom | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Phase I | Phase II | Phase III | Phase IV | ≥90 | <90 | 0~1 | 2 | 3 | 4 | A | B |
| Treatment group | | | | | | | | | | | | | | | |
| NHL | 78 | 41 (23~63) | 45/33 | 4 | 11 | 43 | 20 | 49 | 29 | 20 | 31 | 19 | 8 | 43 | 35 |
| HL | 32 | 40 (20~61) | 19/13 | 2 | 7 | 15 | 8 | 20 | 12 | 7 | 11 | 10 | 4 | 18 | 14 |
| Control group | | | | | | | | | | | | | | | |
| NHL | 52 | 40 (18~57) | 37/15 | 3 | 7 | 29 | 13 | 35 | 17 | 11 | 17 | 15 | 9 | 31 | 21 |
| HL | 22 | 38 (21~57) | 14/8 | 2 | 3 | 10 | 7 | 15 | 7 | 2 | 10 | 6 | 4 | 14 | 8 |

Note: NHL: non hodgkin's lymphoma, HL: hodgkin's lymphoma, M: male, F: female, Symptom of A: there were no fever,emaciation and night sweats Symptom of B: incloud fever, emaciationand night sweats; IPI: international prognostic index.

Australia or other country, there were 30 thousand people suffered from ML each year, and the tendency increased every year. In China, 25 thousand suffered from ML and the number was increasing in recent years [24]. Surgery, radiotherapy, chemotherapy or treatments with traditional Chinese drugs were used in treating ML.

Autologous peripheral blood stem cell transplantation (APBSCT) was important in treatment for ML. However, there was still less report or investigation on the APBSCT treating ML or obtaining high therapeutic effect [25]. The long-term survival rate is still unsatisfactory because of relapsed disease. From January 2000 and December 2009, 110 ML patients in our hospital had received adoptive immunotherapy after APBSCT. They have lower risk of relapse, better long term-survival rate, and higher efficacy than patients received APBSCT only. We will report it as follow.

## Materials and methods

### *Patient characteristics*

110 ML patients (78 non-Hodgkin's lymphoma (NHL), 32 Hodgkin's lymphoma (HL)) received adoptive immunotherapy after APBSCT from January 2000 and December 2009 were the treatment group, 74 ML patients (52 NHL and 22 HL) received APBSCT lonely were the control group. More information are shown in **Table 1**. All MLs were confirmed T-cell lymphomas by morphology and immunohistochemistry. All cases were devided into A group and B group based on B symptoms, which consist of by fever, weight loss and night sweats. All patients had initial staging procedures include complete blood counts, serum biochemistry, LDH level test, erythrocyte sedimentation rate, computed tomography (CT) or MR scan of neck and skull, X ray or CT of chest, B-Ultrasound or CT of abdomen, B-Ultrasound for superficial Lymph Node, bone marrow aspiration and biopsy, except for complete physical examination and sufficient history-taking. Patients were staged according to the Ann Arbor classification.

### *Treatment before transplantation*

Before transplantation, patients with NHL received 2 course of CHOP, TAOP and MEOP sequentially, while patients with NHL received 2 course regimen of ABVD, TAOP and MEOP.

### *Mobilization, collection and preservation of autologous peripheral blood stem cell (PBSC)*

We mobilized the PBSC using chemotherapy combined with recombinant human granulocyte colony stimulating factor (rhG-CSF). More details of collection and preservation of PBSC were shown the reference [1].

### *APBSCT procedure*

All patients received transplant conditioning regimen including total body's irradiation and multidrug chemotherapy ,as follows: 6.0-7.0 Gy total body irradiation (4.5-5.5 Gy on lungs, dose rate <10 cGy/min) on day-5; Vincristine 2 mg and etoposide 200 mg on day -5; mitoxantrone 10 mg on days -5 to -3, Ara-C 1000 mg twice on day -4 and day -3; cyclophosphamide 60 mg/Kg on day -2, nothing on day -1, Stem cells were infused on day 0. The number of infused mononuclear cells were About $3.2\times10^8$-$5.9\times10^8$/Kg body weight, which included $5.7\times10^6$-$9.2\times10^6$/Kg body weight of CD34+ cell.

### *Prevention of complications*

To prevent hepatic veno-occlusive after transplantation by compound Salvia Injection, prostaglandin E and antisterone, to prevent and

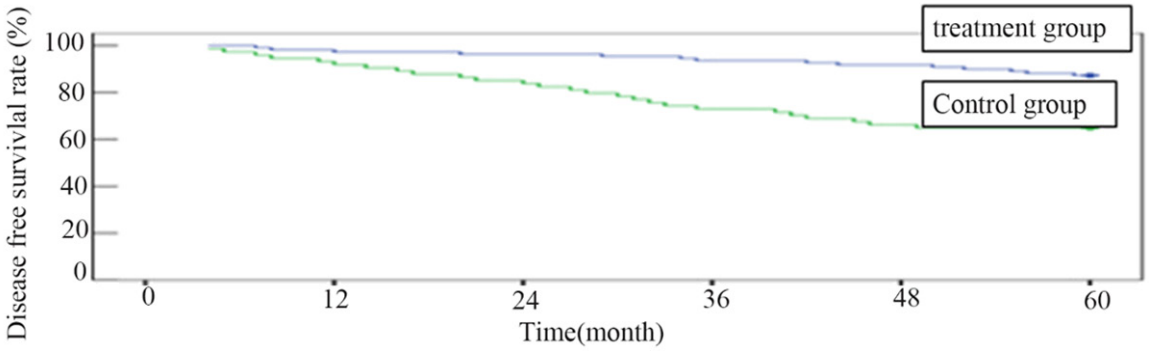


**Figure 1.** Disease free survival curver of two groups.

treat hemorrhagic cystitis by mesana, alkalization of urine, diuretic therapy and so on, bacterial infection by VD antibiotics, fungal infection by VD Fluconazole. platelet were transfused when platelet were less than $20\times10^9$/L, Red Blood Cell were transfused when RBC were less than 80 g/L, hG-CSF 150 ug were used per 12 hours when the nutrophils were 0, IL-1 3mg were used per day on some patients to promote hematopoietic recovery.

*Adoptive immunotherapy after transplantation*

After hematopoietic reconstruction, the patients in treatment group were given six courses adoptive immunotherapy (rhIL-2 100 WU/day for 10 days per month for one course) while the patients as control group were not given immunotherapy.

*Follow-up criteria*

All patients were followed up hospitalized or by telephone for once every 3 months during the first year, every 6 months form the second year and the total followed up time was 5 years.

*Statistical analysis*

Statistical analyses were performed using the SPSS software (version 13.0). $\chi^2$ test were used in efficacy analysis, Kaplan-Meier methods were used in DFS analysis.

## Results

*Hematopoietic restitution and transplant complications*

There was one patient in each group did not get the hematopoietic restitution, one died of hepatic failure 3 months later and one of cerebral hemorrhage 2 months later. Therefore, the overall rate of transplant-related mortality was 1.09%. Granulocytes $\geq0.5\times10^9$/L were reached at days from 10 to 16, white blood cells $\geq 4.0\times10^9$/L were reached at days from 13 to 20, Platelets $\geq50\times10^9$ were reached at days from 21 to 28. The bone marrow pattern was normal 21 to 28 days later. 37 patients got mouth ulcers, which improved after regular treatment for 7-10 days. 12 patients got hemorrhagic cystitis, which improved after hydration, alkalization of urine, the use of mesana. 41 patients got fever with the temperature about 38-39°C, which became normal after antibiotic treatment for 5-7 days. 47 patient got liver dysfunction which were improved after liver protection therapy.

*Total efficacy of two groups*

The complete response (CR) rate of the treatment group and the control group before transplantation was 80.9% and 83.9%, respectively, there is no significant difference between two groups (P>0.05). After 1 years of follow-up, disease free survival (DFS) of the treatment group and the control group were 97.3% (107/110) and 91.9% (68/74), respectively, there is no significant difference between two groups (P>0.05). After 3, 5 years of follow-up, DFS of the treatment group and the control group were 93.6% (103/110) and 73.0% (54/74), 87.3% (96/110) and 64.9% (48/74), respectively, there is significant difference between two groups (P<0.01). DFS rate of two groups shown in **Figure 1**.

*The efficacy of patients in different stages*

The CR rate of patient in stage I/II and III/IV in the treatment group and the control group were

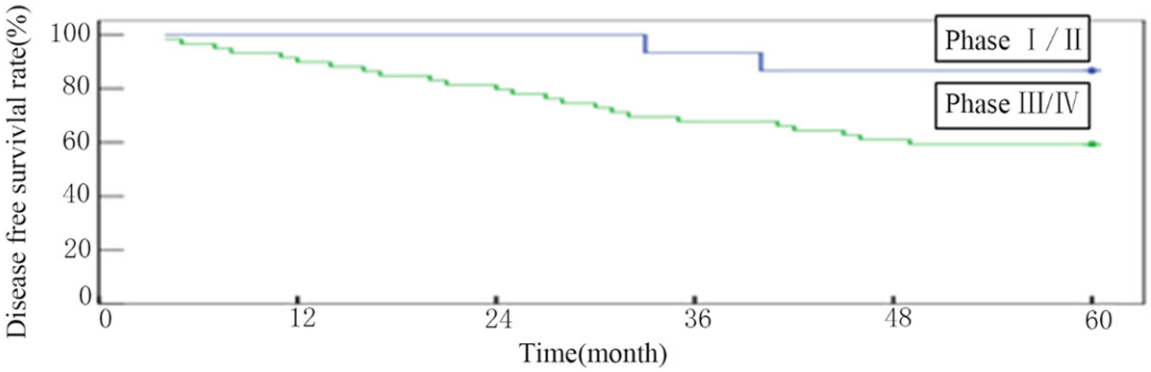


**Figure 2.** Disease free survival curver of phase I/II and III/IV in control group.

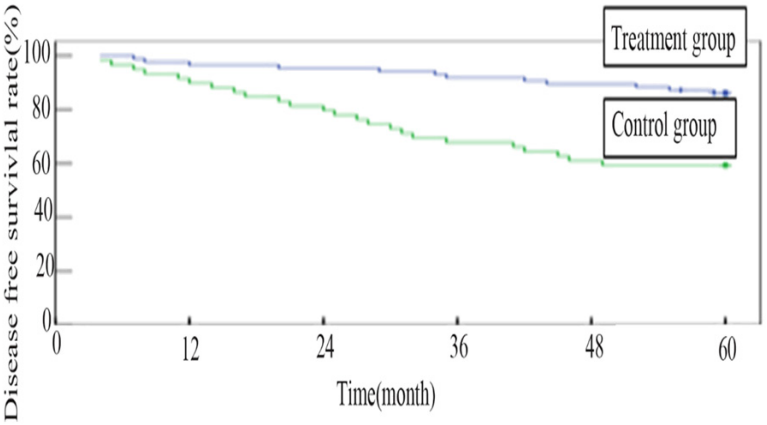


**Figure 3.** Disease free survival curver of phase III/IV in two group.

87.5% and 79.1%, 93.3% and 81.4%, respectively, there is no significant difference between different stages and two groups (P>0.05). For the treatment group, after 1, 3, 5 years of follow-up, DFS of patients in stage I/II and stage III/IV were 100%, 100%, 91.7% and 96.5%, 91.9%, 86.0%, respectively, there is no significant difference between different stages (P>0.05). For the control group, the 1 year DFS rate of patients in stage I/II and stage III/IV were 100% and 93.3%, respectively, there is no significant difference between different stages (P>0.05). the 3,5 years DFS rate of patients in stage I/II and stage III/IV in the control group were 86.7%, 89.8% and 67.8%, 59.3%, respectively, there is significant difference between different stages (P<0.01). For patients in stage I/II, there is no significant difference between the DFS of two groups in 1, 3, 5 years follow-up (P>0.05). For the patients in stage III/IV, there were also no significant difference in DFS between two groups in 1 years follow-up (P>0.05), but there is significant difference in DFS between two groups in 3, 5 years follow-up (P<0.01). DFS of patients in different stages of two groups is shown in **Figures 2** and **3**.

*The efficacy of HL patients*

The CR rate of HL patients in the treatment group and the control group were 87.5% and 86.4%, there is no significant difference between two groups (P>0.05). After 1 years of follow-up, DFS of HL patients in the treatment group and the control group were 100% and 100%, there is no significant difference between two groups (P>0.05). After 3, 5 years of follow-up, DFS of HL patients in the treatment group and the control group were 93.8% (30/32) and 72.7% (16/22), and 84.4% (27/32) and 59.1% (13/22), respectively, there is significant difference between two groups (P<0.05).

*The efficacy of HL patients in different stages*

The CR rate of HL patient in stage I/II and III/IV in the treatment group and the control group were 100% and 82.6%, 100% and 82.4%, respectively, there is no significant difference between different stages and two groups (P>0.05). For the treatment group, after 1, 3, 5 years of follow-up, DFS of HL patients in stage I/II and stage III/IV were 100%, 100%, 88.9% and 100%, 91.3%, 82.6%, respectively. For the control group, after 1, 3, 5 years of follow-up,

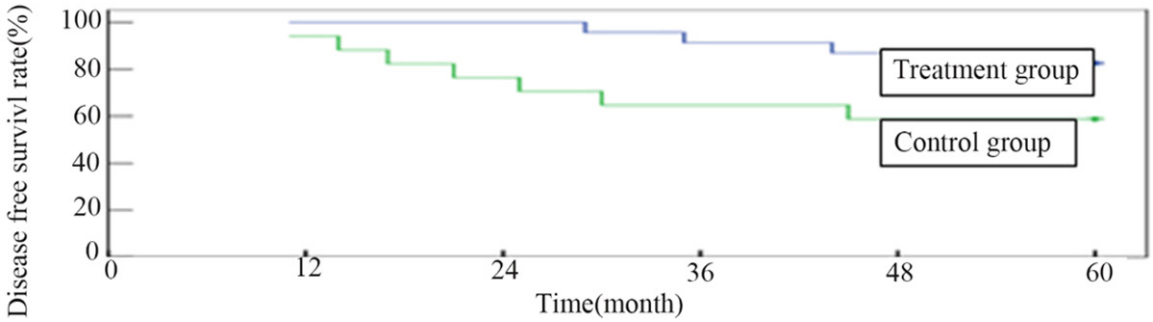


**Figure 4.** Disease free survival curver of phase III/IV of HL in two group.

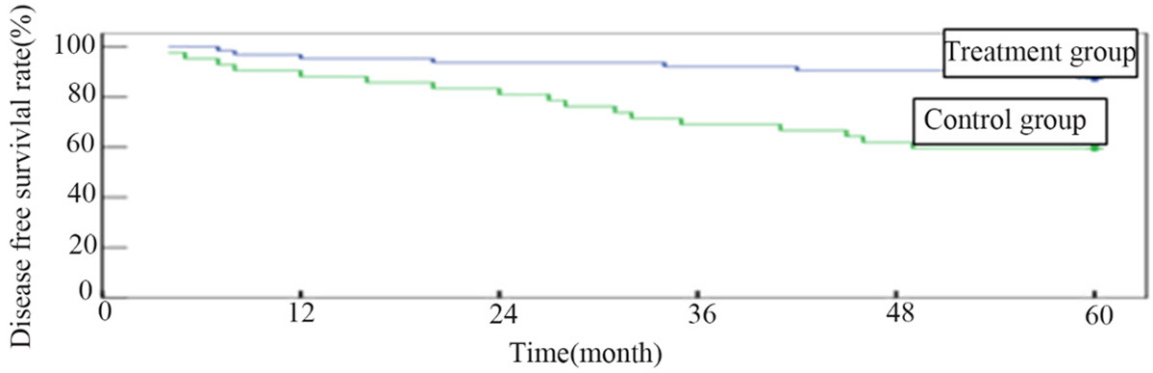


**Figure 5.** Disease free survival curver of phase III/IV of NHL in two group.

DFS of HL patients in stage I/II and stage III/IV were 100%, 100%, 80.0% and 94.1%, 64.7%, 52.9%, respectively.

For HL patients in stage I/II, there is no significant difference between the DFS of two groups in 1, 3, 5 years follow-up (P>0.05). For the HL patients in stage III/IV, there were also no significant difference in DFS between two groups in 1 years follow-up (P>0.05), but there is significant difference in DFS between two groups in 3, 5 years follow-up (P<0.05). It is shown in **Figure 4**.

*The efficacy of NHL patients*

The CR rate of NHL patients in the treatment group and the control group were 78.2% and 82.7%, there is no significant difference between two groups (P>0.05). After 1 years of follow-up, DFS of NHL patients in the treatment group and the control group were 96.2% (75/78) and 90.4% (47/52), there is no significant difference between two groups (P>0.05). After 3, 5 years of follow-up, DFS of NHL patients in the treatment group and the control group were 93.6% (73/78) and 73.1% (38/52), 88.5% (69/78) and 65.4% (34/52), respectively, there is significant difference between two groups (P<0.05).

*The efficacy of NHL patients in different stages*

The CR rate of NHL patient in stage I/II and III/IV in the treatment group and the control group were 80.0% and 90.0%, 77.8% and 81.0%, respectively, there is no significant difference between different stages and two groups (P>0.05). For the treatment group, after 1, 3, 5 years of follow-up, DFS of NHL patients in stage I/II and stage III/IV were 100%, 100%, 93.3% and 95.2%, 92.1%, 87.3%, respectively. For the control group, after 1, 3, 5 years of follow-up, DFS of NHL patients in stage I/II and stage III/IV were 100%, 90.0%, 90.0% and 88.1%, 69.0%, 59.5% respectively. For NHL patients in stage I/II, there is no significant difference between the DFS of two groups in 1, 3, 5 years follow-up (P>0.05). For the NHL patients in stage III/IV, there were also no sig-

nificant difference in DFS between two groups in 1 years follow-up (P>0.05), but there is significant difference in DFS between two groups in 3, 5 years follow-up (P<0.05). It is shown in **Figure 5**.

## Discussion

Malignant lymphoma (ML) are sensitive to chemotherapy and radiotherapy, so their Short-term outcome are better than other malignant tumor. Though 3 years DFS was high to 50% when NHL patients adopted CHOP regimen and HL patients adopted ABVD regimen as first line therapy, local radiotherapy are adopted for specific circumstances. The long-term DFS was only 30%, while other patients died of relapse or progression [2, 3]. Clinical Studies has proved that autologous blood stem cell transplantationin after chemotherapy will improve survival rate than chemotherapy alone [4-6]. The efficacy of APBSCT as consolidation therapy for high-risk patients and as salvage therapy for progressive patients has also been suggested by several studies, but the role of APBSCT in the first-line treatment for primary NHL patients remains controversial [7-9]. Some studies have shown APBSCT should be the standard treatment for the novo patient who did not get remission, Some studies suggested that APBSCT should be the standard treatment for the patients who do not get first remission, patients with chemosensitive relapsed disease, patients with aggressive or advanced disease, and high-risk patient with poor prognosis [10-12]. Though the present results show the efficacy and safety of APBSCT Compared with chemotherapy and radiotherapy in patients with malignant lymphoma, some patients die from relapsed disease. Transplant-related mortality was just 2.7% [13].

Patient relapsed because that even transplantation conditioning including high doses of total body irradiation and chemotherapy can not completely eradicate residual cancer cells in the transplant recipient [14, 15]. Some studies have shown that some treatment like double APBSCT [16, 17], APBSCT followed regular chemotherapy or biotherapy [18], using DC-CIK cells after [19] APBSCT help to prevent of re currence [20]. It also shown that consolidation chemotherapy or local radiotherapy after APBSCT will improve the long-term survival. According To our study, there were no significant difference in CR rate before APBSCT between two groups. APBSCT related mortality was just 1.09%. After 5 years follow up, 3 or 5 year DFS of patients who received IL-2 as the adoptive immunotherapy after APBSCT were higher than patients received APBSCT only. There is no significant difference in DFS between stage I/II patients and stage III/IV patients in the treatment group. But for the control group, there is significant difference in DFS between stage I/II patients and stage III/IV patients in the control group in 3, 5 years follow-up. Significant difference were observed stage III/IV patients between the treatgroup and the control group, which inferred that the patients of stage III/VI benefit significantly. Patients of staged I/II also benefit from APBSCT as the first line therapy for its safety and efficacy.

IL-2 was a type of cytokine that regulates the activities of lymphocytes, that are responsible for immunity. IL-2 also promotes the proliferation and differentiation of T/NK cells and enhances phagocytosis, induces cytokine's secretion, which play an important role in anti-tumor immunity [21]. Nagler [22] et al had shown an advantage in DFS for 109 malignant lymphoma patients who received rIL-2 immunotherapy after APBSCT in comparison with historic controls. These results suggest that rIL-2 is relatively well tolerated. There was a significant enhancement of long term survival of ML patients receiving post-APBSCT immunotherapy. In short, APBSCT were safe for malignant lymphoma, with few and mild complications. Using IL-2 as adoptive immunotherapy after APBSCT would improve DFS significantly, which has a broad scope in future clinical application, It is worth further popularizing.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Hai Bai, Department of Hematology, Lanzhou General Hospital, Chinese PLA, Lanzhou 730050, China. Tel: +86-0931-8994171; Fax: +86-0931-8994171; E-mail: baiahi_bh@163.com

## References

[1] Wang C, Bai H, Xi R, Pan Y, Xu S, Zhang Q, Chen Y and Zhou J. Curative Efficacy for Nasal Type

Extranodal NK/T-Cell Lymphoma by Autologous Peripheral Blood Stem Cell Transplantation after Sequencing Chemotherapy and Radiotherapy. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2013; 27: 1283-1286.

[2] Jabbour E, Hosing C, Ayers G, Nunez R, Anderlini P, Pro B, Khouri I, Younes A, Hagemeister F, Kwak L and Fayad L. Pretransplant positive positron emission tomography/gallium scans predict poor outcome in patients with recurrent/refractory Hodgkin lymphoma. Cancer 2007; 109: 2481-2489.

[3] Shen ZX and Zhu XZ. Maligant lymphoma. Beijing: people's medical publishing house; 2011. pp. 25-28, 345-357.

[4] Haioun C, Lepage E, Gisselbrecht C, Salles G, Coiffier B, Brice P, Bosly A, Morel P, Nouvel C, Tilly H, Lederlin P, Sebban C, Brière J, Gaulard P and Reyes F. Survival benefit of high-dose therapy in poor-risk aggressive non-Hodgkins' lymphoma: Final analysis of the prospective LNH87-2 protocol-A groupe d'etude des lymphomes del'adulte study. J Clin Oncol 2000; 18: 3025-3030.

[5] Guo YG, Xiao Q, Feng ML and Liu L. Clinical analysis of autologouse hematopoietic stem-cell transplantation in 44 patietnts with lymphoma. Chongqingyiokedaxuexuebao 2014; 39: 116-120.

[6] Dhakal S, Biswas T, Liesveld JL, Friedberg JW, Phillips GL and Constine LS. Patterns and timing of initial relapse in patients subsequently undergoing transplantation for Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 2009; 75: 188-192.

[7] McCarthy PL Jr, Hahn T, Hassebroek A, Bredeson C, Gajewski J, Hale G, Isola L, Lazarus HM, Lee SJ, Lemaistre CF, Loberiza F, Maziarz RT, Rizzo JD, Joffe S, Parsons S and Majhail NS. Trends in utilization and survival after autologous hematopoietic cell transplantation in North America from 1995 to 2005: Significant improvement in survival for lymphoma and myeloma during a period of increasing recipient age. Biol Blood Marrow Transplant 2013; 19: 1116-1123.

[8] Chinratanalab W, Reddy N, Greer JP, Morgan D, Engelhardt B, Kassim A, Brandt SJ, Jagasia M, Goodman S, Savani BN. Immunomodulatory nonablative conditioning regimen for B -cell lymphoid malignancies. Exp Hematol 2012; 40: 431-435.

[9] Cai Y, Yang J, Jiang JL, Zhu J and Wang C. High-dose etoposide in mobilization for 40 patients with refractory lymphoma. Zhongguoaizhengzazhi 2014; 24: 750-754.

[10] Vose JM, Carter S, Burns LJ, Ayala E, Press OW, Moskowitz CH, Stadtmauer EA, Mineshi S, Ambinder R, Fenske T, Horowitz M, Fisher R and Tomblyn M. Phase III randomized study of rituximab/carmustine, etoposide, cytarabine, and melphalan (BEAM) compared with iodine-131 tositumomab/BEAM with autologous hematopoietic cell transplantation for relapsed diffuse large B-cell lymphoma: results from the BMT CTN 0401 trial. J Clin Oncol 2013; 31: 1662-1668.

[11] Jantunen E and Sureda A. The evolving role of stem cell transplants in lymphomas. Biol Blood Marrow Transplant 2012; 18: 660-673.

[12] Guo YG, Feng XL, Liu L. Progress of autologous hematopoietic stem cells transplantation in the treatment of lymphoma. Zhongguozuzhigongchengyanjiu 2012; 16: 4323-4328.

[13] Espigado I, Ríos E, Marín-Niebla A, Carmona M, Parody R, Pérez-Hurtado JM, Márquez FJ and Urbano-Ispizua A. High rate of longterm survival for high-risk lymphoma patients treated with hematopoietic stem cell transplantation as consolidation or salvage therapy. Transplant Proc 2008; 40: 3104-3105.

[14] Peterlin P, Leux C, Gastinne T, Roland V, Mahé B, Dubruille V, Delaunay J, Chevallier P, Guillaume T, Blin N, Ayari S, Clavert A, Mohty M, Dousset C, Milpied N, Harousseau JL, Moreau P, Wuilleme S, Moreau A and Le Gouill S.Is ASCT with TBI superior to ASCT without TBI in mantle cell lymphoma patients? Transplantation 2012; 94: 295-301.

[15] Shao LL, Xiao X B, Kaili Zhong KL, Lu Y, Chen XL, Da Y, Liu J, Zhao SH, Ma Y, Yang QS, Su H and Zhang JH. Clinical Observation of 100 Patients with Malignant Lymphoma Treating with Different Preconditioning Regimens Followed by Autologous Hematopoietic Stem Cell Transplantation 100. Zhongguoshiyanxueyexuezazhi 2012; 20: 598-602.

[16] Yu J, Yu L, Liu HC, Yao SX, Lou FD, Zhou Q, Li HH, Bo J, Yu QS, Zhao Y and Zhu HY. Long-term outcome comparison between single and double antologous hematopoietic stem cell transplantation for hematologic malignancies: Data review in 150 cases. Zhongguozuzhigongchengyanjiuyulinchuangkangfu 2007; 11: 4811-4813.

[17] Smith SM, van Besien K, Carreras J, Bashey A, Cairo MS, Freytes CO, Gale RP, Hale GA, Hayes-Lattin B, Holmberg LA, Keating A, Maziarz RT, McCarthy PL, Navarro WH, Pavlovsky S, Schouten HC, Seftel M, Wiernik PH, Vose JM, Lazarus HM and Hari P. Second autologous stem cell transplantation for relapsed lymphoma after a prior autologous transplant. Biol Blood Marrow Transplant 2008; 14: 142-144.

[18] Chen XH, Zhang X, Gao L, Zhang C, Kong FY, Liu H, Gao L, Sun AH, Peng XG and Wang QY. Clinical analysis of non-Hodgkin's lymphoma treated by high dose MTX, autologous peri-

pheral stem celltransplantation and biotherapy for 67 case. Zhongguoshiyongneikezazhi 2007; 27: 1605-1606.
[19] Wang L, Shi CL, Li Y, Yuan CL. Effects of DC-CIK cells on prevention of recurrence of malignant hematopathy after hematopoietic stem cell transplantation. Qingdaodaxueyixueyuanxuebao 2010; 46: 142-144.
[20] Hu K, Wang JJ, Zhao W, Tian L, Wan W and Ke XY. Clinical Observation and Long-time Follow-up of Patients with Malignant Lymphoma treated with Autologous Peripheral Blood Hematopoietic Stem Cell Transplantation. Zhongguoshiyanxueyexuezazhi 2013; 21: 1471-1476.
[21] Zeiser R and Negrin RS. Interleukin-2 receptor downstream events in regulatory T cells: implications for the choice of immunosuppressive drug therapy. Cell Cycle 2008; 7: 458-462.
[22] Nagler A, Berger R, Ackerstein A, Czyz JA, Diez-Martin JL, Naparstek E, Or R, Gan S, Shimoni A and Slavin S. A randomized controlled multicenter study comparing recombinant interleukin 2 (rIL-2) in conjunction with recombinant interferon alpha (IFN-alpha) versus no immunotherapy for patients with malignant lymphoma post autologous stem cell transplantation. J Immunother 2010; 33: 326-333.
[23] Malignant Lymphoma. 2013.
[24] Gianni AM, Siena S, Bregni M, Lombardi F, Gandola L, Di Nicola M, Magni M, Peccatori F, Valagussa P, Bonadonna G. High-dose sequential chemo-radiotherapy with peripheral blood progenitor cell support for relapsed or refractory Hodgkin's disease--a 6-year update. Ann Oncol 1993; 4: 889-91.
[25] Matsuo K, Hamajima N, Hirose K, Inoue M, Takezaki T, Kuroishi T, Tajima K. Alcohol, Smoking, and Dietary Status and Susceptibility to Malignant Lymphoma in Japan: Results of a Hospital-based Case-control Study at Aichi Cancer Center. Jpn J Cancer Res 2001; 92: 1011-1017.