Haploidentical hematopoietic stem cells transplantation for the treatment of medulloblastoma*☆

One case report

Hu Hai-yan, Guo Hong-bo, Wu Bing-yi, Deng Lan, Song Chao-yang, Guo Kun-yuan

Abstract

BACKGROUND: Some reports demonstrated that, autoallergic or hematopoietic stem cells transplantation combined with chemotherapy received good outcomes in treating medulloblastoma, which can prolong survival time of patients. However, whether haploidentical hematopoietic stem cells transplantation can treat medulloblastoma remains poorly understood.
OBJECTIVE: To firstly report a patient receiving haploidentical hematopoietic stem cells transplantation for treating medulloblastoma.
METHODS: A terminal cancer patient with bone matastases successively received six lymphocyte transfusions from an unrelated donor combined with chemotherapy and three haploidentical hematopoietic stem cell transplantations.
RESULTS AND CONCLUSION: The patient presented erythra, accompanied by fever, diarrhea and yellow brown liquid stools, which was considered as graft versus host disease, and treated by urbason, gammaglobulin, CellCept, Prograf, Basiliximab (anti-CD25 antibody), Infliximab (anti-tumor necrosis factor α antibody), effective antibacterial and supportive treatments. After that, the erythra and diarrhea were remised. But the patient died from cerebral hemorrhage. Allogeneic lymphocyte transfusion can kill or damage tumor cells, improve life quality, but the outcome is restrained for patient with a high tumor burden. Immunosuppressant, such as anti-CD25 antibody and anti-tumor necrosis factor α antibody should be timely used in consideration of allogeneic hematopoietic stem cell transplantation.

INTRODUCTION

Medulloblastoma, one of the most common stubborn malignancy tumors in children, often peaks its incidence at age 3 to 10 years with a mean age of 5 years[1-3]. It is highly malignant entities with an inherent tendency to metastasize *via* the cerebrospinal fluid, originating from primitive neuroepithelial cell, situating in the external granular layer of the cerebellum and belonging to the family of central primitive neuroectodermal tumors[4-6]. Approximately 30% of the medulloblastoma was found in children, while medulloblastoma accounted for less than 3% of all of the primary brain tumors in adult with an annual incidence rate of 0.05 per 100 000 per year only. Almost all patients have already had metastatic disease in the spinal cord at the time of first detection on the tumor. Surgical excision combined with craniospinal irradiation([CSI] 54 Gy to the posterior fossa and 36 Gy to the craniospinal axis]) was always the gold standard for treatment of medulloblastoma; however, poor prognosis was concluded and new approaches are needed[7-10]. Despite gradual improvement in the survival rate over the last decade, infants and young children still have a dismal prognosis with poor overall survival and high treatment-related morbidity with CSI as its major causes of high impairment. In order to decrease long-term sequelae caused by central nervous system irradiation in young children with medulloblastoma, most cooperative groups have designed strategies to delay or avoid radiotherapy, based on prolonged conventional chemotherapy. Other worldwide groups have successfully used high-dose chemotherapy combined with autologous stem cell transplantation to increase disease-free survival in patients with such recurrent diseases as medulloblastoma. Clinical studies of non-myeloablative allogeneic hematopoietic stem cell transplantation have demonstrated that donor's lymphocytes transferred with the graft may induce a clinically meaningful antitumor effect (graft-versus tumor) in recipients with hematologic or stubborn tumors refractory to conventional treatments, but few data are available currently in patients with medulloblastoma.

CASE STUDY

In August 2006, a 6-year-old boy presented nausea, vomiting and hyperspasmia accompanied by occipital headaches that increased with exertion. He then developed blurred vision and progressive ataxia. MRI scans of the head revealed a 7 cm × 7 cm mass in the forth-cerebral ventricle. A radical surgery was performed at an outside institution and the pathological evaluation revealed medulloblastoma. The patient was treated with the adjuvant craniospinal irradiation (40 Gy). A part remission was achieved when he was admitted to our institution for relapsed medulloblastoma (stage IV, World Health Organization Classification). The patient refused to move and to be touched for his ostealgia all over the body, especially in the knee joints. His routine blood examination was white blood count (WBC) 3.06×10^9/L, neutrophilic granulocyte 1.57×10^9/L, hemoglobin 44.6 g/L, platelet 31.2×10^9/L, which indicating that red blood cell count (RBC) and thrombocyte transfusions were required. The report of bone marrow aspiration showed the carcinoma cell was more than 50% in nucleated cell. He was so weak that only low-dose chemotherapy could be chosen. He accepted fludarabine (20 mg for 2 days)

Department of Hematology, Zhujiang Hospital, Southern Medical University, Guangzhou 510282, Guangdong Province, China

Hu Hai-yan☆, Doctor, Associate investigator, Department of, Hematology, Zhujiang Hospital, Southern Medical University, Guangzhou 510282, Guangdong Province, China
xuri1104@163.com

Guo Hong-bo☆, Doctor, Associate chief physician, Department of Neurosurgery, Zhujiang Hospital of Southern Medical University, Guangzhou, China
Hongboguo158@126.com

Hu Hai-yan and Guo Hong-bo contributed equally to this paper.

Correspondence to: Guo Kun-yuan, Associate professor, Department of Hematology, Zhujiang Hospital, Southern Medical University, Guangzhou 510282, Guangdong Province, China

Supported by: the National Natural Science Foundation of China, No. 30800486*

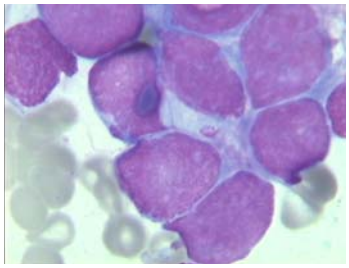
Received: 2010-04-12
Accepted: 2010-05-18
(20100120016/GW)

Hu HY, Guo HB, Wu BY, Deng L, Song CY, Guo KY. Haploidentical hematopoietic stem cells transplantation for the treatment of medulloblastoma: One case report. Zhongguo Zuzhi Gongcheng Yanjiu yu Linchuang Kangfu. 2010;14(32): 6073-6076.

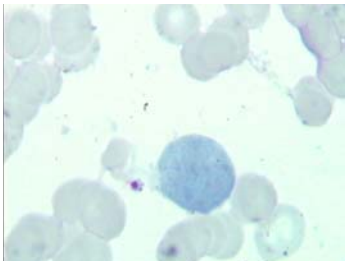
[http://www.crter.cn http://en.zglckf.com]

and methotrexate (5 mg) treatment combined with twice lymphocyte transfusions from unrelated ABO compatibility but HLA mis-matched donor on October 30th, 2007. Symptoms, especially the ostealgia, relieved significantly and he discharged from the hospital. He accepted etoposide (40 mg for 3 days) on November 26th and velcade (0.8 mg) on November 29th and December 3rd, respectively. And then, lymphocyte transfusion from the same donor was performed twice on December 8th and 13th. The patient, getting better and better, could crawl in the bed and stand for a few minutes with weight increase for 2 kg during the treatment. His routine blood examination recovered to WBC 3.06 g/L, GRAN 1.57 g/L, hemoglobin 91.6 g/L, platelet 53.3 g/L. On Dec 30th we gave him etoposide (70 mg for 5 days) and velcade (1 mg) and lymphocyte transfusion from the same donor was performed twice again; meanwhile we gave him rhIL-2 (50 000 IU for 5 days). But aggravated disease was found in January and the patient was admitted to hospital again for short of breath, gaze, clouding of consciousness on February 14th. MRI showed a 2.5 cm ×3 cm mass on the left angle of mandible and metastasis on the right frontal and left temporal lob. The haploidentical hematopoietic stem cell transplantation from his father was performed as the family strongly urged on March 14th. The conditioning regimen included fludarabine (35 mg/m^2 for 4 days, from −10 to −7), busulfanum (15 mg/m^2 for 5 days, from −11 to −7), etoposide (100 mg/m^2 for 5 days), anti-human thymocyte globulin (5 mg/kg for 5 days) and velcade (1 mg for 2 days, −6 day, −5 day).

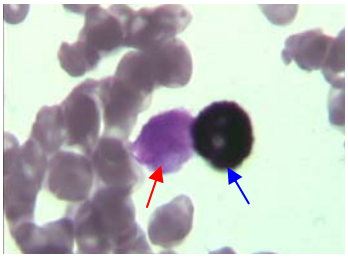
The patient accepted PBSC and bone marrow cell on March 25th and 28th, respectively. Three days later, WBC decreased to almost zero; the patient had diarrhea without fever and the concentration of cyclosporine A was 180 μg/L. Urbason (40 mg) was given by considering the lymphocyte donor was mis-matched; but the patient got a high fever reaching to 39.6 ℃ after 17 days. Hemoculture indicated enterococcus faecalis septicaemia and the symptoms disappeared after effective antibacterial and supportive treatments, but the haematogenesis did not return until April 14th. Peripheral blood stem cell and urbason 240 mg for 2 consecutive days were performed, but hematopoitic reconstitution failed again. On May 1st, we did the third-time transfusion. The conditioning regimen included fludarabine (35 mg/m^2 for 4 d, −5 to 2 d), cyclophosphamide (1.2 g/m^2 for 2 d, −4 d, −3 d; 0.65 g/m^2 for 1 d, −2 d), ciclosporin A (80 mg/m^2 for 3 d, −1 d, 0 d, +1d) and anti-human thymocyte globulin (3 mg/kg for 4 d). Hematopoiesis reconstituted on the 11th day, the routine blood examination described WBC 1.12×10^9/L, hemoglobin 83.2 g/L and platelet 38.9×10^9/L. But grade III GVHD was kept and such symptoms as erythra, serious liquid stools was found; treatment plan was then devised in consultation with pediatrician, digestion physicians, neurosurgeon and the bone marrow transplant team. This plan involved the use of urbason, gammaglobulin, CellCept, Prograf, Basiliximab (anti-CD25 antibody), Infliximab (anti-tumor necrosis factor α antibody); erythra and diarrhea was remised until June 23rd. The patient transferred to general ward; however, the condition was deteriorated in July for cytomegalovirus infection. The haematogenesis was suppressed significantly and the patient died for cerebral hemorrhage (Figure 1).



a: Tumor cell stained by Wright-Giemsa



b: Tumor cell stained negatively with periodic acid staining



c: Peroxidase staining (Red arrow: negatively stained tumor cell; blue arrow: positively stained neutrophil)

Figure 1 Morphological changes of bone marrow

DISCUSSION

Donor's lymphocytes transferred with the allogeneic hematopoietic stem cell transplantation (allo-HSCT) may produce a clinically meaningful antitumor effect (graft-versus tumor) in recipients with stubborn tumors[11-12]. At the beginning, the patient was too week to undergo transplantation, so the treatment plan was low-dose chemotherapy combined with lymphocyte infusion. His mother was under lactation at that time and his father had incompatible blood type with him, so an unrelated donor was chosen in order to enhance the graft-versus-tumor effect by KIR mismatch[13]; however it caused great difficulties for further treatment. Maybe this is the reason for severe graft versus host disease (GVHD) and rejection of the graft at first. For haploidentical bone marrow transplantation, the acute GVHD (aGVHD) is so common that almost all patients have grade II to IV life threatening. The recent experimental data of donor indicate that aGVHD develops in three phases: epithelial-cell injury caused by the conditioning regimen (pre transplant phase), activation of donor T lymphocytes (T-cell activation phase) and the effector phase. Unfortunately, little progress has achieved in the treatment of aGVHD. High-dose steroids are of ten adopted for patients presenting more than grade II tumor; however, 40% of those patients are resistant to this treatment. During the early treatment, the life quality of

patient improved significantly without any GVHD symptoms and the tumor load decreased by bone marrow aspiration, but intracranial metastasis was showed by MRI after infusion for seven times. It is the reason for intracranial metastasis that immune escape was induced by immunoediting after lymphocyte infusion repeatedly. The parents knew the reports of Matsuda[14] and Lundberg[15], in which the child obtained a short-lasting PR following allogeneic hematopoietic SCT for relapsed medulloblastoma, and the other patient achieved CR lasting more than 2 years following allogeneic hematopoietic SCT for recurrent metastatic medulloblastoma, so the parents urged to do allo-HSCT for the boy. As we know, so many data on the effect of HLA mismatching bone marrow transplantation (BMT)[16-17] showed an overall increase of incidence as compared with that on the effect of HLA-identical sibling BMT and the frequency of graft failure increased as donor/recipient HLA disparity increased[18]. It was difficult for us to choose the donor and the conditioning regimen. Considering time and candidate constraints, and the reference to past HSCT experience in our department, thus, his father was selected as his donor. The number of stem cells in the graft was increased to improve the success rate, but it failed in the first two transplantations and the severe GVHD bothered the boy from covering from the whole process. Although successful engraftment occurred on the third time, steroid-refractory aGVHD was still uncontrolled[19]. Of note, interleukin-2 and tumor necrosis factor-αcan lead to cellular activation as well as local tissue damage. There has been a major development in the last few years of monoclonal antibodies that targeted on cytokines[20]. Basiliximab, a chimeric monoclonal antibody, binds with high affinity to the alpha-chain of the interleukin-2 receptor and prevents the formation of the IL-2 binding site[21-22]. Basiliximab is efficient and feasible for steroid-refractory aGVHD and merits further evaluation[23]. Previous studies[24-25] evaluated the response of 17 patients with steroid-refractory aGVHD after related (n=6) or unrelated (n=11) allo-HSCT to basiliximab. Of 17 patients,12 (71%) responded to basiliximab, 9 (53%) had a complete response of aGVHD and 3 (18%) had a partial response. In this case, basiliximab with dose of 10 mg per week was used for 4 times: the patient had partial response; the erythra disappeared but liquid stools were still 5−7 times per day. The treatment combined with infliximab, the humanized monoclonal anti- tumor necrosis factor-α antibody, binds to high-affinity soluble and transmembrane forms of tumor necrosis factor-α and inhibits the binding of tumor necrosis factor-α with its receptors. Tumor necrosis factor-α, secreted mainly by activated mononuclear phagocytes, is the principal mediator of acute inflammation after microbial challenge; besides that, it can also stimulate the recruitment of neutrophils and monocytes, and activate these cells to eradicate microbes. Infiximab has been used in Crohn disease[26] and rheumatoid arthritis[27]. Anti-tumor necrosis factor-α therapy with murine monoclonal antibodies[28] was employed to treat steroid-resistant GVHD and it appeared to be particularly useful with the help of intestinal movement. Couriel and his colleagues[29] reported that a weekly dose of 10 mg/kg infliximab in patients with steroid-refractory GVHD could result in an 80% response rate in 37 patients with gastrointestinal movement. But Marty *et al*[30] reported Infliximab increased risk of non-CandidaIFI in hematopoietic stem cell transplantation recipients with severe GVHD disease, thus, only a dose of 10 mg/kg per month was adopt. The symptom was controlled as soon as the second day infliximab was used and 2 month later, unfortunately, the boy infected by cytomegalovirus, so haematogenesis was suppressed significantly. The boy died from cerebral hemorrhage.

Bias or deficiency of this study

This study firstly report treating medulloblastoma using haploidentical hematopoietic stem cell transplantation. An unrelated donor was selected for lymphocytes infusion, which led to the severe aGVHD and resulted in hematopoitic reconstitution failure.

Clinical application significance

In conclusion, medulloblastoma is high risky and easy metastases. Allo-HSCT is potential a treatment. No report concerning medulloblastoma treated by haploidentical hematopoietic stem cell transplantation was found. Own to the one child policy, related HLA matched donor is difficult to find and haploidentical hematopoietic stem cell transplantation has been accepted gradually, but the incidence of aGVHD is much higher than the other mortality. Thus, more experiments needs to be performed.

REFERENCES

[1] Faria C, Miguéns J, Antunes JL, et al. Pediatric brain tumors: genetics and clinical outcome. J Neurosurg Pediatr. 2010;5(3):263-270.
[2] Serowka K, Chiu Y, Gonzalez I, et al. Central nervous system (CNS) tumors in the first six months of life: the Children's Hospital Los Angeles experience, 1979-2005. Pediatr Hematol Oncol. 2010;27(2):90-102.
[3] Khan S, Evans AA, Rorke-Adams L, et al. Head injury, diagnostic X-rays, and risk of medulloblastoma and primitive neuroectodermal tumor: a Children's Oncology Group study. Cancer Causes Control. 2010.[Epub ahead of print]
[4] Paulino AC, Lobo M, Teh BS, et al. Ototoxicity After Intensity-Modulated Radiation Therapy and Cisplatin-Based Chemotherapy in Children with Medulloblastoma. Int J Radiat Oncol Biol Phys. 2010. [Epub ahead of print]
[5] Klesse LJ, Bowers DC. Childhood medulloblastoma: current status of biology and treatment. CNS Drugs. 2010;24(4):285-301.
[6] Bangaru ML, Chen S, Woodliff J, et al. Curcumin (diferuloylmethane) induces apoptosis and blocks migration of human medulloblastoma cells. Anticancer Res. 2010;30(2):499-504.
[7] Makino K, Nakamura H, Yano S, et al. Population-based epidemiological study of primary intracranial tumors in childhood. Childs Nerv Syst. 2010.[Epub ahead of print]
[8] Srivastava VK, Nalbantoglu J. The cellular and developmental biology of medulloblastoma: Current perspectives on experimental therapeutics. Cancer Biol Ther. 2010;9(11). [Epub ahead of print]
[9] Huse JT, Holland EC. Targeting brain cancer: advances in the molecular pathology of malignant glioma and medulloblastoma. Nat Rev Cancer. 2010;10(5):319-331.
[10] Schmidt AL, Brunetto AL, Schwartsmann G, et al. Recent Therapeutic Advances for Treating Medulloblastoma: Focus on New Molecular Targets CNS Neurol Disord Drug Targets. 2010. [Epub ahead of print]
[11] Secondino S, Pedrazzoli P, Schiavetto I, et al. Antitumor effect of allogeneic hematopoietic SCT in metastatic medulloblastoma, Bone Marrow Transplantation. 2008;42:131-133.
[12] unn GP, Bruce AT, Ikeda H, et al. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol. 2002;3(11):991-998.

[13] Davies SM, Ruggieri L, Defor T, et al. Evaluation of KIR ligand incopatibility in mismatched unrelated donor hematopietic transplants. Blood.2002;100:3825-3827.
[14] Matsuda Y, Hara J, Osugi Y, et al. Allogeneic peripheral stem cell transplantation using positively selected CD34+ cells from HLA-mismatched donors. Bone Marrow Transplant.1998; 21: 355-360.
[15] Lundberg JH, Weissman DE, Beatty PA, et al. Treatment of recurrent metastatic medulloblastoma with intensive chemotherapy and allogeneic bone marrow transplantation. J Neurooncol.1992; 13: 151-155.
[16] Kasamon YL, Luznik L, Leffell MS, et al. Nonmyeloablative HLA-haploidentical bone marrow transplantation with high-dose posttransplantation cyclophosphamide: effect of HLA disparity on outcome. Biol Blood Marrow Transplant. 2010;16(4):482-489.
[17] Spellman S, Warden MB, Haagenson M, et al. Effects of mismatching for minor histocompatibility antigens on clinical outcomes in HLA-matched, unrelated hematopoietic stem cell transplants. Biol Blood Marrow Transplant. 2009;15(7):856-863.
[18] Lee SJ, Klein J, Haagenson M, et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. Blood. 2007;110(13):4576-4583.
[19] Johnston L. Acute graft-versus-host disease: differing risk with differing graft sources and conditioning intensity. Best Pract Res Clin Haematol. 2008;21(2):177-192.
[20] Bay JO, Cabrespine A, Peffault de Latour R. Role of monoclonal antibodies in the treatment of acute graft versus host disease. Bull Cancer. 2007;94(1):33-41.
[21] Funke VA, de Medeiros CR, Setúbal DC, et al. Therapy for severe refractory acute graft-versus-host disease with basiliximab, a selective interleukin-2 receptor antagonist. Bone Marrow Transplant.2006;37(10):961-965.
[22] Przepiorka D, Kernan NA,Ippoliti C, et al. aclizumab, a humanized anti-interleukin-2 receptor alpha chain antibody, for treatment of acute graft-versus-host disease. Blood. 2000; 95: 83-89.
[23] Pasquini R, Moreira VA, Medeiros de CR, et al. Basiliximab–a selective interleukin-2 receptor antagonist–as therapy for refractory acute graft-versus-host disease following bone marrow transplantation. Blood. 2000;96:177a(Abstr. 762).
[24] Schmidt-Hieber M, Fietz T, Knauf W, et al. Efficacy of the interleukin-2 receptor antagonist basiliximab in steroid-refractory acute graft-versus-host disease. Br J Haematol. 2005;130(4):568-574.
[25] Massenkeil G, Rackwitz S, Genvresse I, et al. Basiliximab is well tolerated in the treatment of steroid-refractory acute graft-versus-host disease after allogeneic stem cell transplantation. Bone Marrow Transplant. 2002;30(12):899-903.
[26] Strout MP, Seropian S, Berliner N; Medscape. Alemtuzumab as a bridge to allogeneic SCT in atypical hemophagocytic lymphohistiocytosis. Nat Rev Clin Oncol. 2010. [Epub ahead of print]
[27] Lipsky PE, van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med. 2000;343:1594-1602.
[28] Korngold R, Marini JC, de Baca ME, et al. Role of tumor necrosis factor-alpha in graft-versus-host disease and graft-versus-leukemia responses. Biol Blood Marrow Transplant. 2003;9(5):292-303.
[29] Couriel DR, Hicks K, Ippoliti C, et al. Infliximab for the treatment of graft-versus-host disease in allogeneic transplant recipients: an update [abstract]. Blood. 2000;96:400a.
[30] Marty FM, Lee SJ, Fahey MM, et al. Infliximab use in patients with severe graft-versus-host disease and other emerging risk factors of non-Candida invasive fungal infections in allogeneic hematopoietic stem cell transplant recipients: a cohort study. Blood. 2003;102(8):2768-2776.

*

单倍体相合造血干细胞移植治疗髓母细胞瘤 1 例*☆

胡海燕，郭洪波，吴秉毅，邓　兰，宋朝阳，郭坤元(南方医科大学附属珠江医院血液科，广东省广州市 510282)

胡海燕☆，女，1976 年生，河南省南阳市人，汉族， 2005 年暨南大学毕业，博士， 副研究员，主要从事干细胞分化与发育，肿瘤基因治疗研究。xuri1104@163.com

并列第一作者：郭洪波☆，女，1971 年生，河北省石家庄人，汉族，2005 年南方医科大学毕业，博士，副主任医师，主要从事神经干细胞分化发育研究。

hongboguo158@126.com

通讯作者：郭坤元，副教授，南方医科大学附属珠江医院血液科，广东省广州市 510282

摘要

背景:目前部分国外报道显示，自体及全相合造血干细胞移植联合化疗用于转移髓母细胞瘤有一定疗效，可延长患者生存期。但尚未见 HLA 单倍体相合移植治疗髓母细胞瘤的报道。

目的:首次报道应用单倍体相合造血干细胞移植治疗髓母细胞瘤。

方法:对晚期骨转移的髓母细胞瘤患儿进行连续 6 次无关供者淋巴细胞输注联合低剂量化疗， 3 次单倍体相合骨髓移植治疗。

结果与结论:造血干细胞移植后患儿出现皮疹， 伴发热， 腹泻， 为黄褐色水样便， 考虑为移植物抗宿主病，以甲强龙冲击治疗并用丙种球蛋白增强免疫力， 吗替麦考酚酯、他克莫司抗排斥及口服激素、抗 CD25 单抗、抗肿瘤坏死因子， 并纠酸、维持水电平衡、支持营养等治疗好转出院，后因颅内复发死亡。异基因淋巴细胞输注可杀伤肿瘤细胞，改善患者生存质量，但对于高肿瘤负荷的患者， 效果有限， 如考虑进行异基因干细胞移植， 应注意免疫抑制剂(如 CD25 单抗和肿瘤
坏死因子 a 抑制剂)的及时应用。

关键词:髓母细胞瘤；淋巴细胞输注；单倍体造血干细胞；移植；干细胞移植

doi:10.3969/j.issn.1673-8225.2010.32.041

中图分类号: R394.2　文献标识码: B

文章编号: 1673-8225(2010)32-06073-04

胡海燕， 郭洪波， 吴秉毅， 邓兰， 宋朝阳，郭坤元. 单倍体相合造血干细胞移植治疗髓母细胞瘤 1 例[J].中国组织工程研究与临床康复， 2010，14(32):6073-6076.

[http://www.crter.org http://cn.zglckf.com]

(Edited by Zhao LJ/Wang L)

来自本文课题的更多信息--

基金资助：国家自然科学基金资助(30800486)项目。

利益冲突：课题未涉及任何厂家及相关雇主或其他经济组织直接或间接的经济或利益的赞助。