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Original Article

Analysis of the clinical efficacy of penciclovir in the prevention of viral infection after allogeneic hematopoietic stem cell transplantation

Jia Liu, Peiyan Kong, Lidan Zhu, Shichun Gao, Huanfeng Liu, Lu Wang, Cheng Zhang, Li Gao, Xi Zhang*, Lei Gao*

Medical Center of Hematology, Xinqiao Hospital; State Key Laboratory of Trauma, Burn and Combined Injury, Army Medical University, Chongqing 400037, China.

ABSTRACT

This study aims to retrospectively analyze the efficacy of penciclovir in the prevention of viral infection after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Ninety-six patients with allo-HSCT were enrolled, who were treated at the Medical Center of Hematology of Xinqiao Hospital from June 2020 to September 2021. The experimental and control groups were treated with penciclovir and acyclovir, respectively, to prevent viral infection. By February 2022, the infection rates of cytomegalovirus, BK virus, JC virus, and Epstein-Barr virus (EBV) in the experimental group and the control group were 18.8% and 39.06% (P<0.05), 28.1% and 25% (P>0.05), 6.2% and 7.81% (P>0.05), 21.8% and 23.43% (P>0.05), respectively. The infection-related urinary system symptoms of the experimental group and the control group occurred in 4 and 9 patients, respectively, of which 3 and 9 patients died, respectively. Penciclovir can significantly reduce the cytomegalovirus infection rate after allo-HSCT and has better preventive effects than acyclovir without obvious side effects. The effectiveness and safety of penciclovir will be further verified in the future.

Keywords: penciclovir, allogeneic hematopoietic stem cell transplantation, cytomegalovirus, viral infection

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective treatment for malignant hematological diseases. Viral infection is a common complication after allo-HSCT, and it seriously affects the quality of life and survival rate of patients after transplantation[1]. Cytomegalovirus (CMV), BK virus, JC virus, and Epstein-Barr virus (EBV) are common types of viral infection after allo-HSCT, which can lead to complications such as pneumonia, hemorrhagic cystitis, retinitis, and gastroenteritis, and may endanger the lives of patients in some cases. The prevention and treatment of post-transplant viral infection are important issues after allo-HSCT, and the prevention of viral infection is just as important as the treatment. Currently, acyclovir is used for the prevention of viral infection after allo-HSCT in China

*Corresponding to: Xi Zhang and Lei Gao, Medical Center Hematology, Xinqiao Hospital; State Key Laboratory of Trauma, Burns and Combined Injury, Army Medical University, 83 Xinqiaozheng Street, Shapingba District, Chongqing 400037, China. E-mails: zhangxxi@sina.com and gaolei7765@163.com.

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and other countries. However, the preventive effect is less than optimal, and the incidence rate of CMV infection ranges from 30% to 70%[2–3]. The dosage of acyclovir for the prevention of viral infection is 0.5 g per 8 hours, and high doses of acyclovir can potentially lead to adverse reactions, including acute renal failure. Other drugs used to prevent viral infection after allo-HSCT include ganciclovir and foscarnet sodium; however, their clinical application is limited due to severe hematological toxicity and intractable water and electrolyte disorders[4]. As a new-generation drug for the prevention of CMV infection, letermovir inhibits the cleavage and packaging of viral DNA by binding to and inhibiting CMV viral terminal complexes UL56 and UL89, thereby exerting an antiviral effect[5]. Letermovir was launched in China in July 2022. It is difficult to apply letermovir to the prevention of CMV infection after allo-HSCT on a large scale in clinical practice due to its high price. Therefore, it is necessary to explore effective and cost-effective methods to prevent and treat viral infection after allo-HSCT. A study in China used penciclovir to prevent and treat CMV pneumonia in patients after kidney transplantation, and the results showed that the efficacy of penciclovir was similar to that of ganciclovir, with mild adverse reactions[6]. In this study, penciclovir injection was used to prevent viral infection and the severity of viral infection complications after allo-HSCT, thereby improving the survival rate and quality of life in patients after transplantation. This study provides clinical evidence for the prevention and control of viral infection after allo-HSCT using penciclovir.

MATERIALS AND METHODS

Clinical data and study design

A retrospective analysis was performed, with 32 allo-HSCT patients receiving penciclovir to prevent viral infection between June 2020 and September 2021 and 64 patients receiving acyclovir to prevent viral infection during the same period. The median age of the patients was 33 years (18–64 years), with 67 males and 29 females. There were 42 cases of acute myeloid leukemia (AML), 30 cases of acute lymphoblastic leukemia (ALL), 12 cases of myelodysplastic syndrome (MDS), 9 cases of aplastic anemia (AA), and 3 cases of acute mixed leukemia (MAL). The penciclovir prevention group received intravenous penciclovir (5 mg/kg, 1/12 h), from 7 days post-transplantation to prevent viral infection until 30 days after transplantation, and the control group received acyclovir (5 mg/kg, 1/12 h) from and until the same time points. During this period, the patients in both groups received intravenous injection of human immunoglobulin (0.4 g/kg, 1/week), and after 31 days, patients in both groups were switched to oral acyclovir. This retrospective study was approved by the Ethics Committee of Xinqiao Hospital of Army Medical University.

Transplantation types and pretreatment protocols

Among the transplantation types, 28 cases were with human leukocyte antigen (HLA) matched sibling HSCTs, 42 cases were with HLA haploidentical related HSCTs, 12 cases were with HLA matched unrelated HSCTs, and 14 cases were with 9/10 HLA matched unrelated HSCTs. Busulfan (Bu) and Cyclophosphamide (Cy) (Bu: 0.8 mg/kg, q6 hours × 4 days; Cy: 60 mg/kg × 2 days) were used for HLA matched sibling HSCTs. For HLA haploidentical related HSCTs, semustine (Me-CCNU) + cytosine arabinoside (Ara-C) + Bu + CTX + antithymocyte globulin (ATG) (CCNU: 0.2 g/m^2 × 1 day; Ara-C: 2 g/m^2 × 2 days; Bu: 0.8 mg/kg, q6 hours × 3 days; CTX: 1.8 g/m^2 × 2 days; ATG: 2.5 mg/kg × 4 days) were used. Bu+Cy+ATG (Bu: 0.8 mg/kg, q6 hours × 4 days; Cy: 60 mg/kg × 2 days; ATG: 2.5 mg/kg × 4 days) were used for unrelated HSCTs.

Prevention of graft versus host disease (GVHD)

A cyclosporin (CsA) + mycophenolate mofetil (MMF) + short-term methotrexate (MTX) regimen was used for the prevention of GVHD in HLA matched sibling donor HSCTs or unrelated HSCTs, and a tacrolimus + MMF + short-term MTX regimen was used for HLA haploidentical related donor HSCTs.

Sources of hematopoietic stem cells

The stem cells for 28 HLA matched sibling donor HSCTs and 26 unrelated HSCTs were derived from donor peripheral blood stem cells. The stem cells for the HLA haploidentical related donor HSCTs were derived from donor peripheral blood stem cells and bone marrow stem cells.

Statistical analysis

Data processing and statistical analysis were performed using SPSS V26 software. The *t* test was used to compare clinical quantitative data, and the Pearson chi-square test was used to analyze the qualitative data. The difference in clinical efficacy between the two groups was compared using an analysis of variance. $P<0.05$ was considered statistically significant.

RESULTS

Baseline conditions of patients

There were no significant differences in sex, age, diagnosis, or types of transplantation between the two groups (***Table 1***).

Hematopoietic reconstruction

Hematopoiesis was successfully reconstructed in all 96 patients. The median time for neutrophil reconstitution in 32 patients in the penciclovir prevention group was 15+ (11+ – 29+) days, and the median time for platelet reconstitution was 18+ (12+ – 38+) days. In the control group (acyclovir), the median time for neutrophil reconstitution in 64 patients was 16+ (13+ – 26+) days, and the median time for platelet reconstitution was 18+ (13+ – 35+) days. There were no significant differences between the two groups (P>0.05). Neutrophils and platelets were successfully implanted in all patients in both groups.

Incidence of viral infection

Among the 32 patients in the experimental group, there were 6 cases of CMV infection (18.8%), 9 cases of BK virus infection (28.1%), 2 cases of JC virus infection (6.2%), and 7 cases of EB virus infection (21.8%). The median onset times of virus infection were 48.5+ days for CMV infection, 42+ days for BK virus infection, 44.5+ days for JC virus infection, and 52+ days for EB virus infection. Among the patients with viral infection, 4 cases exhibited viral infection-related urinary system symptoms, 2 cases exhibited secondary leukopenia and thrombocytopenia, and the remaining patients exhibited viremia alone. Twenty-six patients survived, and 6 patients died. Among the 64 patients in the control group, there were 25 cases (39.06%) of CMV infection, 16 cases (25%) of BK virus infection, 5 cases (7.81%) of JC virus infection, and 15 cases (23.43%) of EB virus infection. The median onset times of virus infection were 33+ days for CMV infection, 33+ days for BK virus infection, 32.5+ days for JC virus infection, and 42+ days for EB virus infection. Fifty-five patients survived, and 9 patients died. Among the patients with viral infection, 9 patients had viral infection related urinary system symptoms, 4 patients had secondary leukopenia and thrombocytopenia, and 2 patients had CMV pneumonia. The above symptoms of the patients were controlled within 2 to 4 weeks. The chi-square test analysis indicated that the prophylactic use of penciclovir significantly reduced the incidence of CMV infection (P<0.05) and that there was no significant difference in the incidence of BK, EB, and JC virus infection between the two groups (P>0.05) (***Table 2***).

GVHD occurrence and survival

Among the 32 patients in the experimental group, 5

Table 1 **Baseline data of the two groups of patients**

	Experimental group	Control group	*P* value
Sample size (patients)	32	64	
Sex			0.08
Male	26	41	
Female	6	23	
Age (years)	33.66±10.35	37.62±12.91	0.14
Diagnosis			0.15
Acute myeloid leukemia	12	30	
Acute lymphocytic leukemia	11	19	
Aplastic anemia	4	5	
Myelodysplastic syndrome	3	9	
Acute mixed lineage leukemia	2	1	
Transplant type			0.67
All matched sibling donor	7	21	
HLA haploidentical sibling donor	20	22	
HLA matched unrelated donor	3	9	
HLA 9/10 matched unrelated donor	2	12	
Sex of donor and recipient			0.65
Male for male	14	25	
Female for female	3	12	
Male for female	3	11	
Female for male	12	16	

Table 2 **Viral infection in the two groups of patients**

Virus type	Experimental group (*n*=32)	Control group (*n*=64)	*P* value
CMV	6	25	0.045
BKV	9	16	0.745
JCV	2	5	0.784
EBV	7	15	0.865

CMV: cytomegalovirus; BKV: BK virus; JCV: JC virus; EBV: Epstein-Barr virus.

patients developed grade Ⅰ–Ⅱ aGVHD, and 1 patient developed grade Ⅲ aGVHD. Among the 64 patients in the control group, 10 patients developed grade Ⅰ–Ⅱ aGVHD, 3 patients developed grade Ⅲ aGVHD, and 1 patient developed grade Ⅳ aGVHD. As of December 2021, among the 32 patients in the experimental group, 29 patients were alive, of whom 5 patients relapsed and 3 patients died (2 patients died of disease relapse and 1 patient died of severe pulmonary infection). The 2-year overall survival (OS) rate was 90.6%, the hazard ratio (HR) was 1.3352 (95% confidence interval [CI] 0.3810–4.6793, *P*>0.05; ***Fig. 1***), the disease-free survival (DFS) rate was 81.3%, and the HR was 1.1757. (95% CI 0.4613–2.9967, *P*>0.05; ***Fig. 2***). Among the 64 patients in the control group, 55 patients survived, of whom 11 patients relapsed and 9 patients died (5 patients died of disease recurrence and 4 patients died of severe lung infection). The 2-year OS rate was 85.9%, the HR was 0.7490 (95% CI 0.2137–2.6249, *P*>0.05), the DFS rate was 76.6%, and the HR was 0.8506 (95% CI 0.3337–2.1679, *P*>0.05).

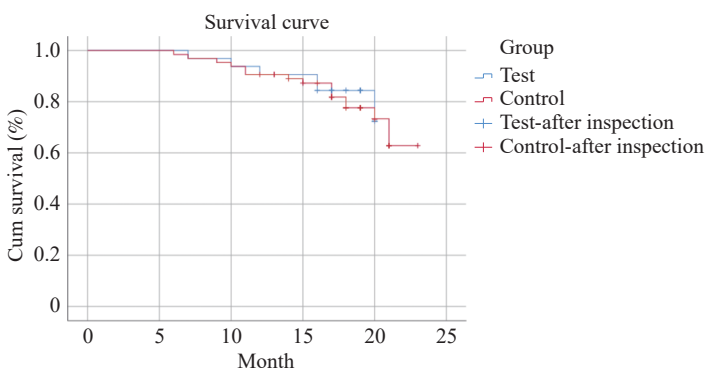

Fig. 1 **Two-year OS of patients in the two groups**

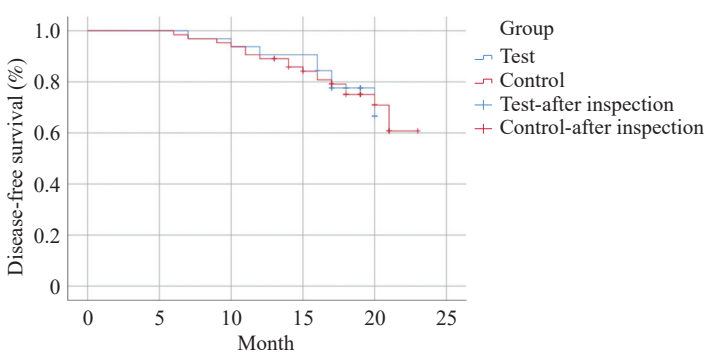

Fig. 2 **Two-year DFS of patients in the two groups**

Adverse effects

During the observation period, there were no adverse reactions such as study drug-related gastrointestinal reactions and liver or kidney dysfunction.

DISCUSSION

Viral infection is a common complication after allo-HSCT, which seriously affects the quality of life and survival of patients after transplantation, with CMV

infection accounting for the highest incidence. For individuals with normal immune function, CMV infection is usually asymptomatic or accompanied with mild flu-like symptoms. However, for patients who receive allo-HSCT, CMV infection may cause serious clinical complications due to severe immunosuppression[7–8]. If not treated in a timely manner, CMV infection can develop into corresponding organ diseases, leading to severe complications and even death in some cases[9]. In addition, CMV has been proven to be associated with the occurrence of GVHD, both of which can be mutually risk factors, increasing the difficulty of treatment[10]. CMV infection is defined as the isolation of virus or detection of viral proteins or nucleic acids in any body fluid or tissue specimen. After infecting the human body, CMV can remain latent in the body for an extended time. When immune function is severely weakened, latent virus replicates actively, causing relevant clinical symptoms, called CMV disease[11]. Clinically, CMV disease can manifest as pneumonia, gastroenteritis, encephalitis, retinitis, nephritis, cystitis, myocarditis, or pancreatitis, among which pneumonia and retinitis are the most common diseases[12–13].

The incidence of BK virus infection is also high after allo-HSCT. BK virus is a human polyoma virus that is usually acquired at a young age and is latent in multiple organs of human body including the kidney and urothelial cells. More than 90% of healthy adults are believed to be positive for BK virus nucleic acid. Normally, people with normal immune function will not experience related clinical symptoms. However, approximately 50% of patients after allo-HSCT develop BK virus infection, with hemorrhagic cystitis (HC) being the most common complication after infection. The likelihood of HC in patients positive for urinary BK nucleic acid is 4 times as high as that of patients with negative results[14–15].

Currently, acyclovir is the widest prescribed drug for the prevention of post allo-HSCT viral infection in China and abroad. However, the preventive effect is unsatisfactory and the incidence of CMV is between 30% and 70%. Ganciclovir and foscarnet sodium are effective in treating CMV infection after allo-HSCT. However, the adverse reactions of these two drugs are relatively high. The main adverse reactions of ganciclovir are bone marrow suppression and hepatic and renal impairment. The adverse reactions of foscarnet sodium are renal dysfunction and electrolyte disturbance[16–19]. Letermovir is a non-nucleoside virus terminase enzyme complex inhibitor that acts on the late stage of viral replication by binding to and inhibiting the viral terminase enzyme complex. It is used to prevent CMV infection and CMV diseases in CMV-seropositive patients receiving allo-HSCT[20]. *In vitro* and mouse model studies have shown that compared with ganciclovir, letermovir has an antiviral activity approximately 1000 times higher and is highly specific for HCMV, with no significant activities against other herpes viruses[21–22]. Because letermovir was recently launched in China, there have been no real-world studies of the use of letermovir in the Chinese population; as well as being new drug, the drug is expensive and has a small target population.

Penciclovir is an acyclic guanosine analog antiviral drug with a structure similar to acyclovir, and it has inhibitory effects on a variety of viruses. It has a long metabolic half-life, is easily taken up by cells, and has the potential to replace acyclovir to prevent viral infection. In virus-infected cells, viral thymidine kinase phosphorylates penciclovir to penciclovir monophosphate, which is then converted to penciclovir triphosphate by cellular kinases, which inhibits viral DNA synthesis and replication, thus imparting antiviral functions. Penciclovir that has not been monophosphorylated can directly prevent further elongation of the viral DNA chain[23]. Our center used penciclovir to prevent viral infection after allo-HSCT. The results showed that the CMV infection rate was lower in the treatment group than that in the acyclovir prevention group. There was no significant difference in the BK virus, JC virus and EB virus infection rates, and the hematopoiesis of all enrolled patients was successfully reconstructed. Neither viral infection-related deaths nor drug-related adverse reactions occurred. The preliminary evidence shows the efficacy of penciclovir in preventing viral infections after allo-HSCT. Its efficacy and safety should be further verified through multicenter, prospective, randomized, and controlled clinical studies. From the results, we also found that the median onset times of all 4 viral infections in the penciclovir group were longer than those in the acyclovir group. In addition, the median onset times of all 4 viral infections in the penciclovir group were far away from the treatment period of penciclovir, but occurred after oral acyclovir. It is worth investigating whether continual use of penciclovir can provide better prevention against viruses, not just CMV. In the future, a new clinical study will be designed to extend the practical time of penciclovir and to observe whether it can further reduce the risk of viral infection.

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