

Effect of Recombinant Human Interleukin-11 on Oral Mucositis Associated with Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract: Background: Hematopoietic stem cell transplantation gives new life to malignant hematologic patient. However, oral mucositis caused by graft-versus-host disease affects the quality of life of patients. Objective: To observe the efficacy of recombinant human interleukin-11 in the treatment of allogeneic hematopoietic stem cell transplantation associated with oral mucositis. Methods: 54 patients requires an allogeneic hematopoietic stem cell transplantation in patients with hematological clinical observation research, the control group was 0.05% acetic acid chloride solution is folinic acid joint and diluent containing wash, the experimental group on the basis of the join recombinant human interleukin - 11 atomization and contain gargle, comparing curative effect, the ulcer healing time and pain, anxiety and depression scores, as well as oral infections. Results: the efficacy of recombinant human interleukin-11 treatment group was better than that of control group ($X^2=4.43$; $P=0.035$); Nebulized inhalation and gargle containing recombinant human interleukin-11 significantly reduced the mean healing days of oral ulcers (Experimenta group A vs. control group C, $P=0.05$, $P=0.004$, $P=0.000$). Experimental group B vs. control group C, $P=0.045$, $P=0.005$, $P=0.000$) and can reduce the occurrence of pain and bad mood. Conclusion: recombinant human interleukin-11 is effective in the treatment of oral mucositis associated with allogeneic hematopoietic stem cell transplantation. It can effectively shorten the course of disease and reduce the incidence of oral infection, anxiety and depression while reducing the pain of patients.

Keywords: Recombinant Human Interleukin-11, Oral Mucositis, Malignant Hematologic

1. Introduction

Hematopoietic stem cell transplantation is currently an important approach to treat malignant hematologic diseases [1]. According to the source of stem cells, there are allogeneic hematopoietic stem cell transplantation (allo-HSCT) and autologous hematopoiesis (auto-HSCT). Allogeneic hematopoietic stem cell transplantation is currently the only way to cure malignant hematological diseases. Oral mucositis (OM), an inflammatory and ulcerative reaction of the oral mucosa is the most common complications of allo-HSCT. The incidence of OM varies from 43.5% and 85.7% in domestic studies, and the onset time is 5-7 days after reinfusion of the graft [2, 3]. The pain caused by OM is the most direct

subjective experience of the patient and seriously affect oral eating, and further lead to the occurrence of unpleasant emotions such as malignant malnutrition, anxiety and depression. In addition, the onset time of Allo-HSCT-related OM is myelosuppression-neutropenia after transplantation. The ulcer wound of oral mucosa is easy to become the channel of pathogen invasion, and it increases the chance of infection. Therefore, it is important to carry out OM-related predictive nursing for patients with hematological diseases who underwent allo-HSCT. At present, the clinical nursing for OM includes routine oral cleaning care, 0.05% acetic acid chloride solution and folinic acid diluent containing wash after MTX treatment, but the incidence of OM is still high. Many studies have shown that interleukin-11 has anti-inflammatory effects

and can selectively reduce the expression of proinflammatory cytokine TNF, IL-1 and interferon. It let cells to enter the cell cycle from the quiescent phase, promote cell proliferation and inhibit apoptosis [4, 5]. Recently, domestic and international scholars have found that interleukin-11 can treat oral ulcers caused by intensive radiotherapy for nasopharyngeal cancer and reduce the risk of apoptosis. In addition, nebulized inhalation of recombinant human interleukin 11 is also effective in improving oral mucositis, relieving pain, and improving ulcer healing time. The effect is superior to that of some mixtures containing multivitamins and procaine. [6] There are still few reported studies on the use of rhIL-11 for the prevention and treatment of allo-HSCT-related OM. Therefore, we observed the efficacy of rhIL-11 in the treatment of oral mucositis associated with allogeneic hematopoietic stem cell transplantation.

2. Information and Method

2.1. General Information

Select 54 patients with hematological diseases who underwent allogeneic hematopoietic stem cell transplantation in our hospital from January 2018 to December 2019 as research objects. They include different hematological disease types: acute leukemia 38, myelodysplastic syndrome 10, aplastic Anemia in 6 cases. Inclusion criteria: Diagnosed by bone marrow puncture and bone marrow biopsy, and there was no oral mucositis and no other treatment measures were taken before allogeneic hematopoietic stem cell transplantation. Exclusion criteria: patients with autoimmune related diseases, communication difficulties, psychiatric disorders, incompatibility, financial incompatibility and patients who could not undergo allogeneic hematopoietic stem cell transplantation. According to the different treatment methods, we divided the patients into experimental group A, experimental group B, and control group C, each with 18 cases, 10 men in experimental group A. There were 10 males and 8 females in group A, 7 males and 11 females in test group B, aged between 12 and 56 years with an average of (44 ± 11) years, while in the control group C, here were 10 males and 8 females, aged between 21 and 56 years, with an average of (47 ± 9) years. There was no significant difference in age and sex among the three groups.

2.2. Evaluation of Oral Ulcer

According to the World Health Organization (WHO) Oral mucositis criteria, oral mucosal ulcers are clinically evaluated as grade 0-IV. [7] Grade 0: no abnormality of the oral mucosa; Grade I: Oral mucosa has 1-2 ulcers smaller than 1.0cm, erythema, slightly painful, does not affect eating; Grade II: 1 ulcer larger than 1.0 cm and several small ulcers in the mucosa, painful, the patient can still eat; Grade III: 2 ulcers in the oral mucosa ulcers larger than 1.0 cm and several small ulcers, increased pain, only fluid diet; Grade IV: 2 or more ulcers in

the oral mucosa ulcers or fused ulcers larger than 1.0 cm are painful and cannot eat.

2.3. Treatment

Experimental group A Patients contain gargled with 0.9% normal saline during allogeneic hematopoietic stem cell transplantation. When the patients developed oral mucositis, we treated the patients with recombinant human interleukin 11 nebulized inhalation joint folic acid diluent gargle. The recombinant interleukin-111.5mg added to 0.9% normal saline 50ml to form a reagent which placed in the refrigerator at 4°C for standby. They carried nebulized inhalation out 10ml/time, 3 times a day.

Experimental group B Patients contain gargled with 0.9% normal saline during allogeneic hematopoietic stem cell transplantation. When the patients developed oral mucositis, contain gargled the recombinant human interleukin 11 joint folic acid diluent. The recombinant interleukin-111.5mg added to 0.9% normal saline 50ml configured into a mixture, stored in a refrigerator at 4°C. Gargle 10ml/time, 3times /day for 2-3min each time.

Control group C Patients gargled with 0.9% normal saline before the development of oral mucositis and, when the patient develops oral mucositis, gargled with 0.05% acetic acid chloride solution and joint folic acid diluent, 10ml/time, 3 times a day, 2-3min each time.

2.4. Methods for Assessing the Effectiveness of Treatment

According to references, citing the Mouth Ulcer Observation Table, statistics on the general condition of patients, transplant pretreatment protocols, the occurrence of mouth ulcers and the healing time, extent of mouth ulcers, presence of oral infections (including purulent and fungal infections), pain scores, anxiety scores, depression scores and feeding status. Efficacy criteria: (1) effective: ruddy oral mucosa, ulcer relieved by 2 grades; (2) effective: ulcer relieved by 1 grade; (3) ineffective: ulcer had no improvement or progression.

2.5. Statistical Methods

We performed statistical analysis using SPSS 20.0 statistical software. Chi-square test was used for counting data, and t-test was used for measurement data.

3. Results

3.1. The Curative Effect of Oral Ulcer Among the Three Groups (Table 1)

All the three groups showed different curative effects, and the curative effects of experimental group A and experimental group B were better than those of the control group C, but there was no statistical difference between experimental group A and experimental group B.

Table 1. Comparison of curative effect of oral ulcer among 3 groups.

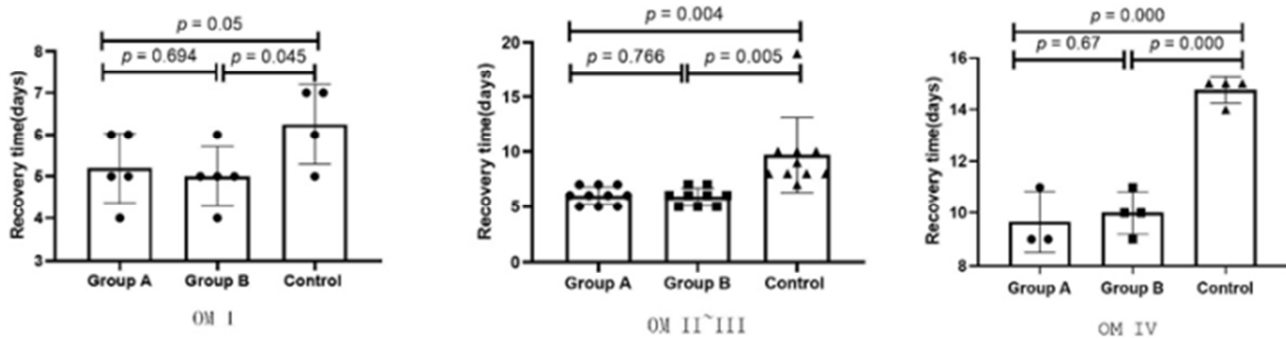
Group	Cases	markedly effective	effective	ineffective	effective rate
A	18	11	6	1	94%
B	18	10	7	1	94%
C	18	7	5	6	67%

$\chi^2=4.43$; $P=0.035$.

3.2. Ulcer Healing Time in Different Degrees Among the Three Groups (Table 2, Figure 1)

Table 2. Comparison of healing time of oral ulcer in 3 groups (d , $\bar{x} \pm s$).

Group	Cases	Average healing days		
		I	II~III	IV
A	18	5.20±0.87	6.00±0.81	9.67±1.15
B	18	5.00±0.70	5.89±0.78	10.00±0.81
C	18	6.25±0.95	9.70±3.43	14.75±0.50

**Figure 1.** Comparison of healing time of oral ulcer in 3 groups.

Compared with the control group, the average healing days of I, II~ III and IV oral ulcers in experimental group A and experimental group B were significantly lower than those in the control group C. (experimental group A vs. control group C, $P= 0.05$, $P=0.004$, $P= 0.000$; experimental group B vs. control group C, $P=0.045$, $P=0.005$, $P=0.000$). There was no significant difference in oral ulcer healing time between group A and group B. (experimental group A vs. The experimental group B was 0.694, 0.766, 0.67).

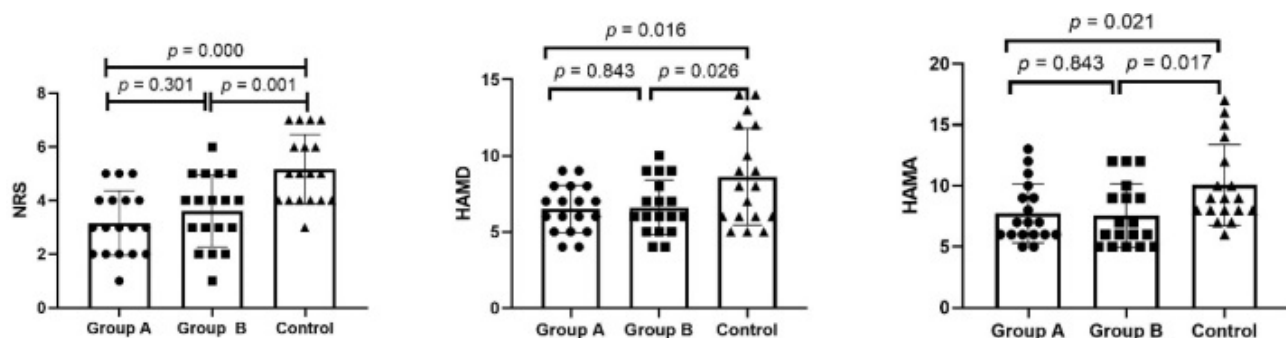
3.3. Pain, Anxiety and Depression Scores Among 3 Groups (Table 3, Figure 2)

Compared with control group C, experimental group A and experimental group B NRS, HAMD and HAMA scores were significantly lower (experimental group A vs. control group C, $P=0.000$, $P=0.016$, $P=0.021$); experimental group B vs. Control group C, $P=0.001$, $P=0.026$, $P=0.017$), both nebulized

and gargled recombinant human interleukin-11 can relieve the pain brought about by OM and to some extent reduce the occurrence of anxiety and depression in patients; in addition. Further comparative analysis revealed that there was no significant difference in Hamilton depression (HAMD), Hamilton anxiety (HAMA) and numerical rating scale (NRS), scores between experimental group A and experimental group B (experimental group A vs. experimental group B, $P= 0.301$, $P= 0.843$, $P= 0.843$).

Table 3. Comparison of HAMD, HAMA and NRS scores of three group (score, $\bar{x} \pm s$).

Group	NRS score	HAMD score	HAMA score
A	3.17±1.20	6.50±1.54	7.72±2.42
B	3.61±1.33	6.61±1.78	7.56±2.59
C	5.17±1.29	8.61±3.18	10.06±3.31

**Figure 2.** Comparison of pain, anxiety and depression scores among 3 groups.

3.4. Oral Infection in Three Groups (Table 4)

Table 4. Comparison of patients with oral infection in 3 groups.

Group	No infection (casas)	Infection (cases)
A	17	1
B	17	1
C	14	4

$\chi^2 = 2.09$; $P = 0.148$.

Nebulized inhalation and gargling of recombinant human interleukin-11 could reduce the probability of oral suppurative infection and fungal infection to some extent, but the difference was not statistically significant.

4. Discussion

Hematopoietic stem cell transplantation is an important treatment for malignant hematological diseases, among which allogeneic hematopoietic stem cell transplantation is currently the only way to cure malignant hematological diseases.

The HLA matched sibling donor (MSD)-HSCT is the best therapeutic option for patients with malignant hematological disorders, and in recent years, with the clinical promotion of unrelated donor unrelated donor (URD)-HSCT, haploidentical (haplo) -HSCT and umbilical cord blood transplantation (UCBT) and improvement of the efficacy, the overall survival time of patients with blood disorders prolonged [8].

While achieving prolonged survival, patients still face numerous transplant-related complications, such as graft-versus-host disease (GVHD), oral mucositis (OM), hemorrhagic cystitis (HC) closely relates the above to the quality of life of patients after transplantation, with OM being the most common during allo-HSCT Complications throughout the 2 stages of transplantation and post-transplantation, with the incidence of OM reported in national studies varying from 43.5% to 85.7%, the time of onset is between 5-7 days after graft reinfusion and is an inflammatory and ulcerative response of the oral mucosa [2]. The mechanism of allo-HSCT-related OM is extremely complex. Numerous previous studies have shown that pre-transplantation pretreatment with high-dose methotrexate (HD-MTX) is the main reason for the high incidence of oral mucositis. Therefore, folinic acid diluent is used in different ways to prevent toxicity [9]. Although the use of folinic acid diluent for prophylactic toxicity antagonism has achieved some efficacy, the incidence of OM remains high. [9] In addition, acute and chronic mucosa-associated GVHD caused by allogeneic graft re-infusion is another important cause of OM [10]. Transfusion of HLA matched or partially matched hematopoietic stem cell results in the short-term release of enormous amounts of interleukin family inflammatory factors and complements a large number of inflammatory mediators' further damage the mucosa, and the numerous side effects of glucocorticoids limit their use in the treatment

of OM 15. The pain caused by OM is the most direct subjective experience of the patient, which severely affects oral eating and further lead to the occurrence of unpleasant emotions such as malignant malnutrition, anxiety and depression; in addition, In addition, the onset time of Allo-HSCT-related OM is myelosuppression-neutropenia after transplantation. The ulcer wound of oral mucosa is easy to become the channel of pathogen invasion, and it increases the chance of infection. Therefore, predictive OM-related care of patients with hematologic disorders who undergo allo-HSCT is essential.

Interleukin-11 (IL-11) is a multipotent cytokine derived from fibroblasts and bone marrow stromal cells that directly stimulates Hematopoietic stem cells and megakaryocyte precursor cells promote platelet production and commonly used clinically to treat thrombocytopenia after myelosuppression [11]. In addition, IL-11 can modulate the activity of non-hematopoietic cells, promote proliferation and partially inhibit the proliferation of mucosal stromal cells apoptosis, which may play a role in protecting basal cells during radiotherapy [12].

It has been found that recombinant human interleukin-11 in the treatment of chemotherapy-induced oral mucositis in nasopharyngeal carcinoma with significant efficacy, both nebulization and gargling of the rhIL-11-containing mixture could prevent the progression of oral mucositis [6]. For pain relief, it is more effective than that of mixtures containing procaine hydrochloride, gentamicin sulfate and multivitamins [13]. There are still no reports of recombinant human interleukin-11 being used in the treatment of allo-HSCT-related OM. Through the clinical observation of 54 patients with hematological diseases in allo-HSCT, it was found that aerosol inhalation or gargling rhIL-11 diluent combined with folinic acid diluent was more effective in the treatment of Allo-HSCT related OM than 0.05% chlorhexidine acetate solution joint folinic acid diluent contain gargle. rhIL-1 can shorten the average healing days of oral ulcers of various degrees and speed up ulcer healing. Aerosol inhalation or gargling rhIL-11 can relieve the chief complaint of pain, reduce the occurrence of anxiety, depression and other unpleasant emotions after the occurrence of OM, and reduce the probability of oral bacterial or fungal infection to a certain extent. There was no significant difference between aerosol inhalation and rhIL-11 diluent gargle.

5. Conclusion

To sum up, recombinant human interleukin-11 is effective in the treatment of oral mucositis associated with allogeneic hematopoietic stem cell transplantation. It can shorten the course of OM, relieve pain and reduce the occurrence of oral infection, anxiety and depression. It is helpful to improve the quality of life of patients with hematological diseases after transplantation, which is worthy of clinical promotion.

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Author Yu Ding and Xiuling Chen are the co-first authors of this paper in no particular order. Due to they have made equally important contributions to the design, experiment, data collation and writing of this paper.

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