Clinics in Oncology

Research Article
Published: 03 Dec, 2022

Intravenous Immunoglobulin: An Effective Adjunct Therapy for Acute Myeloid Leukemia Patients with Neutropenia and Infection

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Abstract

Objectives: Acute Myeloid Leukemia (AML) patients undergoing intensive chemotherapy have a high risk for infection. Reportedly Intravenous Immunoglobulin (IVIg) could improve immune function and significantly reduce febrile episodes and febrile days in pediatric patients with AML and infection. To investigate the adjunct therapeutic effect of IVIg on adult patients with AML, we carried out this study.

Methods: We retrospectively analyzed 138 adult patients with AML who had neutropenia and infection after chemotherapy. Among them, 62 patients got IVIg treatment and 76 did not (serving as controls).

Results: Between two groups there were no differences in the French-American-British classification (FAB) classification, risk status, therapy stage, chemotherapy, duration of neutropenia, site of infection and central venous catheter. But febrile days were significantly decreased in IVIg group relative to the control group (P<0.001).

Discussion: This suggests that IVIg may be an effective adjunct therapy for adult patients with AML who have neutropenia and infection after intensive chemotherapy.

Keywords: Intravenous Immunoglobin; Febrile Days; Neutropenia; Infection; Acute Myeloid Leukemia

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Received Date: *15 Nov 2022*
Accepted Date: *29 Nov 2022*
Published Date: *03 Dec 2022*

Citation:
Shen Y, Bai J, Yang Y, Wang F, He A. Intravenous Immunoglobulin: An Effective Adjunct Therapy for Acute Myeloid Leukemia Patients with Neutropenia and Infection. Clin Oncol. 2022; 7: 1971.

ISSN: 2474-1663

Introduction

Acute Myeloid Leukemia (AML) has a deregulated proliferation of immature myeloid progenitors, leading to the accumulation of leukemic cells in the bone marrow and inhibition of normal hematopoiesis [1]. Intensive chemotherapy is an important treatment for AML patients and it could induce serious neutropenia which could lead to infection. Severe infection can influence patients' tolerance of chemotherapy, prolong their hospital stays and increase the risk of mortality. Although advances in antimicrobial prophylaxis decreased the disease severity and improved the survival rate, the infection-related complications were still the major causes of mortality in AML patients [2].

Recent evidence suggests that utilization of Intravenous Immunoglobulin (IVIg) could decrease the occurrence of infection significantly in Chronic Myeloid Leukemia (CML) and Multiple Myeloma (MM) [3]. What's more, IVIg could significantly reduce febrile episodes and febrile days in pediatric patients with AML and infection [4], but the effect of IVIg on adult AML patients with neutropenia and infection is still unclear. This study was to evaluate the value of IVIg in alleviating infected episode of adult AML patients with neutropenia after chemotherapy.

Material and Methods

Patients

Approval for this analysis was obtained from the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University (Ethics number: 2016225). All the patients provided written informed consent prior to the initiation of the IVIg therapy. A total of 279 AML patients who received intensive chemotherapy and got fever at least lasting for one day from January 2011 to March 2018 were included in this retrospective analysis. Patients were diagnosed as M3 (n=13), the

duration of neutropenia less than Seven days (n=87) and fever caused by the original disease (n=41) was excluded. The data for 138 patients were used for the subsequent analyses. Among them, 62 patients were treated with IVIg (IVIg group) and 76 were not (control group) (Figure 1). We also divided 137 patients as 3 subgroups according to therapy stage, induction, consolidation and relapse subgroup, respectively.

Inclusion criteria: a) Neutropenia lasting more than seven days, b) Infection indicators: Fever during neutropenia (axillary temperature ≥ 38.0°C for at least one day), and clinical signs of infections (e.g., hypotension, tachypnea or tachycardia), or laboratory results of infection (e.g., an increase in c-reactive protein levels) or microbiological findings.

Exclusion criteria: a) Patients with M3 because of the totally different chemotherapy regimen, b) Neutropenia lasting less than seven days, c) Fever caused by original disease.

Neutropenia was defined as an absolute neutrophil count less than 500 cells/mcL. All patients had a confirmed diagnosis of AML according to the French-American-British (FAB) classification and an affirmatory risk status on the basis of National Comprehensive Cancer Network (NCCN) guidelines.

IVIg regimen

Patients received IVIg (200 mg/kg per day, days 1 to 3 or 100 mg/kg per day, days 1 to 5) with the start of finding evidence of infection after getting informed consent.

Chemotherapy regimens

Induction chemotherapy was consisted of anthracic line combined cytarabine (pirarubicin 25 mg/m^2 per day, days 1 to 3, idarubicin 12 mg/m^2 per day, days 1 to 3 or mitoxantrone 10 mg/m^2 per day, days 1 to 3; cytarabine 100 mg/m^2 per day, days 1 to7) and HA (homobarringtonie 1 mg/m^2 per day, days 1 to 3; cytarabine100 mg/m^2 per day, days 1 to 7). Consolidation chemotherapy contained a high-dose cytarabine (3 g/m^2, q12h, days 1 to 3) for patients <60 years old. For the patients who were 60 years or older, we chose intermediate-dose cytarabine (1 g/m^2, q12h, days 1 to 3) combined with pirarubicin (25 mg/m^2/day, days 1 to 3) or mitoxantrone (10 mg/m^2 per day, days 1 to 3). Relapse chemotherapy was mainly priming induction region, including FLAG (fludarabine 30 mg/m^2 per day, days 1 to 4; cytarabine100 mg/m^2 per every 12 h, days 1 to 4; colony stimulating factor 5 ug/kg by subcutaneous injection, days 1), GAA (colony stimulating factor 5 ug/kg by subcutaneous injection, days 1 to 14; cytarabine 10 mg/m^2 per day by subcutaneous injection, days 1 to 14; aclarubicin 15 mg/m^2 per every two days, days 1 to 9), and GHA (cytarabine 7.5 mg/m^2 per day by subcutaneous injection, days 1 to 14, homoharringtonine 1.5 mg/m^2 per day, days 1 to 14, and colony stimulating factor 5 ug/kg by subcutaneous injection, days 0 to 14).

Antibiotic policy

According to NCCN Guidelines, we adopt antimicrobic prophylaxis regularly to treat the patient's receiving chemotherapy when their neutrophil counts were <500 cells/mcL. If they were infected and the pathogen was not detected, we used empirical antibiotics and if the pathogen was detected and clear we used sensitive antibiotics for those patients' receiving chemotherapy. The common agents we used were cephalosporins, imipenem-cilastatin (500 mg IV, 6 h), vancomycin (15 mg/kg IV, 12 h) and biapenem (300 mg/dose IV, 8 h). And we adopted sensitive antibiotics according to the medicine sensitive experiment when the pathogens were detected.

Antifungal policy

All patients with AML received fluconazole (400 mg per day PO), voriconazole (200 mg per day PO) or it raconazole (200 mg per day PO) prophylaxis during neutropenia after chemotherapy. Voriconazole (loading dose 6 mg/kg IV, 12 h at first day, maintenance dose 4 mg/kg IV, 12 h), micafungin (100 mg per day IV), caspofungin (50 mg per day IV) or amphotericin B liposome (1 mg to 3 mg per day IV) were initiated when fungal infection was proved or suspected.

Statistical analysis

We compared baseline characteristics, fever days, infection with a detected pathogen and length of hospitalization between IVIg group and control group. Patient baseline characteristics were compared using *t*-test for continuous variables, chi-square tests for categorical variables, respectively. All tests were two-sided, and P<0.05 were normally considered significant. All statistical analyses were performed with Statistical Product and Service Solutions (SPSS) Statistics for Windows, Version 18.0 (IBM Corp. Armonk, NY, USA).

Results

Patients' characteristics

Table 1 shows the baseline characteristics of both groups. About 51% of IVIg group and 47% of the control group were male patients (P=0.732). The median age was 44 years for the IVIg group and 48 years for the control group (P=0.303). FAB classification showed no difference between two groups (P=0.385), as well as risk status (P=0.541). The component part of therapy stage, including induction, consolidation and relapse, had no gap between two groups (P=0.167). As for chemotherapy, more than 25% patients got anthracycline and cytarabine and 35% of patients got middle or high-dose cytarabine in each group. Median day for the duration of neutropenia was 10 in IVIg group and 11.5 in the control group (P=0.059). Classification of infection sites between two groups demonstrated no difference (P=0.383). The proportions of central venous catheter implantation were not significantly different between the groups (85.5 *vs.* 81.6%, P=0.648), so as the number of the usage of the laminar flow room (P=0.609).

Infection-related data

As shown in Table 2, median of febrile days between two groups were significantly different (2 *vs.* 5, P<0.001), and the febrile days of IVIg group were apparently decreased. Infection with detected pathogen was about 39% in IVIg and 37% in the control group, but the category of the detected pathogen had no difference between two groups (P=0.365). About 40% to 60% patients had a mixed pathogen infection in each group. The duration of hospitalization between two groups had no difference either (P=0.787).

In a stratified analysis, we put the patients into three subgroups as induction, consolidation and relapse subgroup, according to chemotherapy stage, and observed the influence of IVIg on febrile days in three subgroups respectively. The results showed that IVIg reduced febrile days markedly in induction and consolidation subgroups (P=0.034, P<0.001 respectively). A shorter febrile day was also found in IVIg group of relapse subgroup, but P value showed no difference (P=0.355) (Table 3). In all cases treated with IVIg, we haven't found obvious side effect and death yet.

Discussion

We report the results of a retrospective, single-institution analysis

Table 1: Demographic and baseline characteristics.

Characteristics	IVIg group	Control group	P value
Number of patients	62	76	
Gender, no (%)			0.732
Male	32 (51.6)	36 (47.4)	
Female	30 (48.4)	40 (52.6)	
Age (years)			0.303
mean ± SD	40.9 ± 2.3	44.1 ± 2.1	
Median (Range)	44 (18-75)	48 (18-79)	
FAB classification, no (%)			0.385
M1	3 (4.8)	4 (5.3)	
M2	7 (11.3)	15 (19.7)	
M4	27 (43.5)	36 (47.4)	
M5	24 (38.7)	21 (27.6)	
M6	1 (1.6)	0 (0)	
Risk status, no (%)			0.541
Favorable-risk	20 (32.3)	31 (40.8)	
Intermediate-risk	35 (56.4)	36 (47.4)	
Poor-risk	7 (11.3)	9 (11.8)	
Therapy stage, no (%)			0.167
Induction	17 (27.4)	32 (42.1)	
Consolidation	38 (61.3)	35 (46.1)	
Relapse	7 (11.3)	9 (11.8)	
Chemotherapy			0.204
Anthracycline and cytarabine	17 (27.4)	30 (39.5)	
Homobarringtonie and cytarabine	0 (0)	2 (2.6)	
Middle and high-dose cytarabine	38 (61.3)	35 (46.1)	
Priming induction region	7 (11.3)	9 (11.8)	
Duration of neutropenia (days)			0.059
mean ± SD	11.0 ± 0.7	12.7 ± 0.6	
Median (range)	10 (7-28)	11.5 (7-27)	
Site of infection, no (%)			0.383
Respiratory system	31 (50.0)	48 (63.2)	
Gastrointestinal tract and anal abscesses	6 (9.7)	4 (5.3)	
Urinary system	1 (1.6)	1 (1.3)	
Skin and soft tissue	2 (3.2)	1 (1.3)	
Venous catheter	0 (0)	1 (1.3)	
Oral mucosa and teeth	5 (8.1)	1 (1.3)	
Bloodstream	3 (4.8)	3 (3.9)	
Multiple sites	9 (14.5)	13 (17.1)	
Other sites	2 (3.2)	0 (0)	
Unspecified	3 (4.8)	4 (5.3)	
Central venous catheter, no (%)	53 (85.5)	62 (81.6)	0.648
Laminar flow room, no (%)	29 (46.8)	32 (42.1)	0.609

FAB: French-American-British classification; SD: Standard Deviation

investigating the effects and benefits of IVIg treatment in a cohort of AML patients with infection due to chemotherapy-induced neutropenia. The therapy and supportive care were provided to both groups according to NCCN guidelines.

Table 2: Infection-related data.

Characteristics	IVIg group	Control group	P value
Febrile days*			<0.001
mean ± SD	3.3 ± 0.4	6.3 ± 0.5	
Median (range)	2 (1-14)	5 (1-20)	
Infection with detection of pathogen, no (%)	24 (38.7)	28 (36.8)	0.365
Gram-positive	3 (12.5)	3 (10.7)	
Gram-negative	3 (12.5)	4 (14.3)	
Fungal	5 (20.8)	2 (7.1)	
Viral	2 (8.3)	0 (0)	
Other pathogen	1 (4.2)	1 (3.6)	
Mixed infection	10 (41.7)	18 (64.3)	
Duration of hospitalization (days)			0.787
mean ± SD	21.6 ± 0.60	21.8 ± 0.52	
Median (range)	21 (14-30)	21 (13-32)	

SD: Standard Deviation; * P<0.05

Table 3: Differences of the disease stage on the fever days between groups.

	Fever days, mean ± SD		
	Induction *	Consolidation *	Relapse
IVIg group	5.0 ± 1.0	2.2 ± 0.3	5.8 ± 1.4
Control group	8.0 ± 0.8	4.9 ± 0.5	7.7 ± 1.3
P value	0.034	<0.001	0.355

SD: Standard Deviation; *P<0.05

Our data confirmed that IVIg is an effective adjunct therapy for AML patients who got neutropenia and infection after chemotherapy. This finding is in accordance with previous studies on MM and CML [3].

Intensive chemotherapy is the standard therapy for AML nowadays, but it has a serious adverse side-effect, neutropenia, which may lead to severe infection. Besides, it can lead to a growing population of patients with deficits in humoral and cell-mediated immunity [5,6], which may accelerate the development of infection [7]. The related study shows the rate of infection of AML after intensive chemotherapy is about 79% [8]. Lots of factors can contribute to the infection, such as hospital-independent exposure to infectious agents, and comorbidities before admission [9], Central Venous Catheter (CVC) [5,9,10] and length of hospital stays after admission [11].

Severe infections do not only contribute to mortality, but also prolong hospitalization, decrease the tolerance of chemotherapy, lead to complications, decrease quality of life and require the administration of toxic antimicrobial compounds [2]. Therefore, it is necessary to control infection effectively and timely to help patients get over the dangerous period as soon as possible. Survival through the infectious period is not only the important guarantee for follow-up treatment of AML patients, but also the condition for Hematopoietic Stem Cell Transplantation (HSCT) in the future.

Intravenous Immunoglobulin (IVIg), a polyclonal IgG purified from pooled plasma samples of thousand healthy donors [12], could block Fc receptor, neutralize autoantibody, inhibit complement and modulate cytokine and cytokine antagonist production [13-15]. It was approved to prevent and treat infection in the first years of the last century [16]. Nowadays, it was used widely in human disorders and immune reconstitution, such as primary immunodeficiency and

some autoimmune diseases [17]. Even though the clinical studies demonstrating their efficacy and safety are relatively small, IVIg has been proposed as adjuvant therapy for sepsis [18]. Recent studies showed IVIg could improve B cell function [19], restore humoral immunity [20] and influence T cell proliferation, survival and function [13]. A small sample retrospective analysis showed that IVIg therapy reduced febrile episodes and febrile days significantly in AML pediatric patients who got infected [4], and the similar results were found in CLL and MM [3]. What' more, IVIg has a role in restricting the fungal burden and their clearance [21]. So, we tried IVIg therapy as an adjunct therapy to treat adult AML patients with neutropenia and infection after intensive chemotherapy, and the results showed that IVIg could decrease the febrile days effectively. However, whether the earlier IVIg used as an adjunct therapy, the better the prognosis would be, needs further investigation.

In our study, the related factor that may give rise to infection and fever showed no difference between IVIg and control group, such as age, FAB classification, risk status, duration of neutropenia and CVC.

Febrile day is an indirect index of the duration and severity of infection. We found IVIg could decrease the febrile day obviously for AML patients who got infected during neutropenia after chemotherapy. So, we think adjunct IVIg therapy might help us control infection effectively. According to therapy stage, we divided all patients to three subgroups, induction, consolidation and relapse. The reduced febrile days by IVIg were found in induction and consolidation subgroups, but not in relapse subgroup. The possible reason we think is the stubborn condition and the difficulty of obtaining Complete Remission (CR) again for relapse patients, and another reason could be resulted from the relatively small sample size.

Concerning microbiological findings, IVIg did not influence the category of detected pathogen between 2 groups, which may be explained by that IVIg regulate the immunity of patients to fight for infection but not the specific pathogen to act on [22]. The most common type was mixed infection, bacterial and fungal together. The position of infection is mainly focused on the respiratory tract, followed by multi-site infection. However, IVIg had no influence on hospitalization in this study.

Neutropenia is the most common side effect of chemotherapy. In this study, we chose the patients whose duration of neutropenia lasting more than seven days according to the previous investigation [23], to ensure that every patient had the same chance to get infected. The less duration of neutropenia was found in IVIg group, but there was no significant difference between IVIg and the control group. Therefore, IVIG might have contributed to reducing the severity of neutropenia, it does not prevent its occurrence in AML patients [24].

Our study had several limitations. First, this is a retrospective analysis with small sample size, so further prospective trials are warranted. Second, IVIg was initiated just when adult AML patients got an infection after chemotherapy, so the efficiency of IVIg prophylaxis still needs further investigation.

In summary, we showed that the utilization of IVIg as an adjunct therapy could decrease the febrile days significantly in adult AML patients with infection and neutropenia after chemotherapy.

Acknowledgement

We are grateful to Professor Wenjiang Li for the revision support.

References

1. Herv E, Dombret CG. An update of current treatments for adult acute myeloid leukemia. Blood. 2016;127(1):53-61.
2. Gupta A, Singh M, Singh H, Kumar L, Sharma A, Bakhshi S, et al. Infections in acute myeloid leukemia: An analysis of 382 febrile episodes. Med Oncol. 2010;27(4):1037-45.
3. Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O. Immunoglobulin prophylaxis in chronic lymphocytic leukemia and multiple myeloma: Systematic review and meta-analysis. Leuk Lymphoma. 2009;50(5):764-72.
4. Gebauer E, Tomic J, Stevanovic S. Intravenous immunoglobulin in the treatment of infections in children with acute leukemias. Med Pregl. 1994;47(1-2):52-5.
5. Kuo F, Wang S, Shen C, Ma Y, Ho T, Chen J, et al. Bloodstream infections in pediatric patients with acute leukemia: Emphasis on gram-negative bacteria infections. J Microbiol Immunol Infect. 2015;50(4):507-13.
6. Reilly A, Kersun LS, Luning Prak E, Boyer J, McDonald K, Jawad A, et al. Immunologic consequences of chemotherapy for acute myeloid leukemia. J Pediatr Hematol Oncol. 2013;35(1):46-53.
7. Raanani P, AGMP, Ben-Bassat I, Leibovici L, Shpilberg O. Immunoglobulin prophylaxis in hematological malignancies and hematopoietic stem cell transplantation. Review. Cochrane Database Syst Rev. 2008;4.
8. Bainschab A, Quehenberger F, Greinix HT, Krause R, Wölfler A, Sill H, et al. Infections in patients with acute myeloid leukemia treated with low-intensity therapeutic regimens: Risk factors and efficacy of antibiotic prophylaxis. Leukemia Res. 2016;42:47-51.
9. Kugler E, Levi A, Goldberg E, Zaig E, Raanani P, Paul M. The association of central venous catheter placement timing with infection rates in patients with acute leukemia. Leuk Res. 2015;39(3):311-3.
10. Del PM, Buccisano F, Maurillo L, Venditti D, Cefalo M, Sarlo C, et al. Infections increase the risk of central venous catheter-related thrombosis in adult acute myeloid leukemia. Thromb Res. 2013;132(5):511-4.
11. Rajendranath R, Balasubramaniyum V, Vijayakumar V, Ganesan P, Tenali GS. Factors predicting outcome in high-risk febrile neutropenia in patients receiving intensive chemotherapy for acute sleukemia: A prospective, observational study from South India. Indian J Cancer. 2014;51(4):481-6.
12. Schroeder HW, Cavacini L. Structure and function of immunoglobulins. J Allergy Clin Immun. 2010;125(2):S41-52.
13. Afonso AB, João C. The production processes and biological effects of intravenous immunoglobulin. Biomolecules. 2016;6(1):15.
14. Schwab I, Nimmerjahn F. Intravenous immunoglobulin therapy: How does IgG modulate the immune system? Nat Rev Immunol. 2013;13(3):176-89.
15. Durandy A, Kaveri SV, Kuijpers TW, Basta M, Miescher S, Ravetch JV, et al. Intravenous immunoglobulins--understanding properties and mechanisms. Clin Exp Immunol. 2009;158(1):2-13.
16. Eibl MM. History of immunoglobulin replacement. Immunol Allergy Clin North Am. 2008;28(4):737-64.
17. Radosevich M, Burnouf T. Intravenous immunoglobulin G: Trends in production methods, quality control and quality assurance. Vox Sang. 2010;98(1):12-28.
18. Di Rosa R, Pietrosanti M, Luzi G, Salemi S, D'Amelio R. Polyclonal intravenous immunoglobulin: An important additional strategy in sepsis? Eur J Intern Med. 2014;25(6):511-6.
19. Afonso AB, Justo LN, Queiros AC, Fesel C, Cabral MS, Silva MG, et al. Treatment with low doses of polyclonal immunoglobulin improves B cell function during immune reconstitution in a murine model. J Clin Immunol. 2013;33(2):407-19.

20. Carbone J, Sarmiento E, Del PN, Rodriguez-Molina JJ, Navarro J, Fernandez-Yañez J, et al. Restoration of humoral immunity after intravenous immunoglobulin replacement therapy in heart recipients with post-transplant antibody deficiency and severe infections. Clin Transplant. 2012;26(3):277-83.

21. Elluru SR, Kaveri SV, Bayry J. The protective role of immunoglobulins in fungal infections and inflammation. Semin Immunopathol. 2015;37(2):187-97.

22. Eibl MM, Wedgwood RJ. Intravenous immunoglobulin: a review. Immunodefic Rev. 1989;1 Suppl:1-42.

23. Pohlen M, Marx J, Mellmann A, Becker K, Mesters RM, Mikesch J, et al. Ciprofloxacin versus colistin prophylaxis during neutropenia in acute myeloid leukemia: Two parallel patient cohorts treated in a single center. Haematologica. 2016;101(10):1208-15.

24. Lemos S, Jacob CM, Pastorino AC, Castro AP, Fomin AB, Carneiro-Sampaio MM. Neutropenia in antibody-deficient patients under IVIG replacement therapy. Pediatr Allergy Immunol. 2009;20(1):97-101.