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Efficacy and safety of different chemotherapy regimens combined with thalidomide in the treatment of diagnosed HIV-associated diffuse large B-cell lymphoma

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ABSTRACT

Objective: To investigate the short-term efficacy and safety of different chemotherapy regimens combined with thalidomide, in the treatment of low-income patients with newly diagnosed HIV-associated diffuse large B-cell lymphoma.

Methods: A retrospective analysis was performed on 42 patients with HIV-DLBCL who were admitted to the Infectious Diseases Department of Yunnan Provincial Infectious Diseases Hospital from January 2018 to December 2020. 14 cases (including 1 case in stage II and 13 cases in stage III/IV) were treated with R-CHOP, 24 cases (including 1 case in stage II and 23 cases in stage III/IV) were treated with R-DAEPOCH, and 4 cases (including 1 case in stage II and 3 cases in stage III/IV) were treated with EPOCH. All patients were treated with thalidomide. The ART regimen was adjusted. At least 1 and up to 6 intrathecal injections were given during chemotherapy, and cotrimoxazole was taken orally to prevent infection. The clinical efficacy was evaluated after 4 cycles of chemotherapy, and adverse events were evaluated at each cycle of chemotherapy.

Results: All patients received 1–8 cycles of chemotherapy. CR (64.2 %) was achieved in 9 patients in R-CHOP group, and 5 patients died. In the R-DAEPOCH group, 17 patients achieved CR (70.8 %) and 7 died. In the EPOCH group, 2 patients reached CR (50 %) and 2 died. The main adverse reactions were grade II and above myelosuppression.

Conclusion: Combined treatment with thalidomide can improve the prognosis of low-income patients with newly diagnosed HIV-DLBCL.

1. Introduction

Acquired HIV syndrome (acquired immunodeficiency syndrome, human immunodeficiency virus (HIV) Infection AIDS) patients are more likely than the immunocompetent population to develop tumors [1], and the incidence of lymphoma is 60 to 200 times that of the general population. HIV-associated diffuse large B-cell lymphoma (HIV-DLBCL) is the most common type of HIV-associated NHL (HIV-NHL), accounting for 45 % of HRL [2]. It has become the most common subtype of malignant tumor in HIV-infected patients, often accompanied by low CD_4 T lymphocyte counts. Compared with Lymphoma in immunocompetent, HIV-DLBCL has a more acute onset, more rapid disease progression, and a higher mortality rate [3]. Therefore, early diagnosis and combined treatment can improve the survival rates of these patients. However, Because HIV-DLBCL patients have lower incomes compared to the general population, they cannot afford some of the costs of drugs, as a result, delay ART treatment resulting in suppressed immune status of patients.In addition, ART drugs often interact with chemotherapy drugs, so the selection and balance of antiviral therapy and tumor chemotherapy are a major clinical challenge.Consequently,further exploration of cost-effective, safe and effective combination treatment schemes is needed. To this end, we retrospectively analyzed the short-term efficacy and safety of different chemotherapy regimens combined with thalidomide in the treatment of low-income patients with newly diagnosed HIV-DLBCL patients, We explored effective treatment regimens suitable for these patients.

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2. Materials and methods

Retrospective analysis was conducted on 42 patients with newly diagnosed HIV-DLBCL in Yunnan Infectious Disease Hospital from January 2018 to December 2020. Informed consent was obtained from all patients for the scientific use of their clinical data.

Inclusion criteria were as follows: (1)Confirmed positive HIV-1 antibodies in blood; Whether the patient is on ART or not;(2)The first pathological diagnosis was diffuse large B-cell lymphoma with immunohistochemical CD20 positive;(3)Age≥18 years old and ≤75 years old, No restrictions on men and women. All patients have not received targeted therapy, chemotherapy, or stem cell transplantation.

2.1. General clinical data

Among the 42 patients, 31 patients were males and 11 patients were females; The age ranged from 22 to 73 years, with a median age of 46 years. There were 34 patients without steady occupation and 8 patients with fixed occupations. 38 patients were treated with ART at the first diagnosis of lymphoma, and only 4 cases were not treated with ART. 32 patients had CD_4 T lymphocyte counts less than 200/μl, and 10 patients had CD_4 T lymphocyte count more than 200/μl. 2 cases were complicated by hepatitis (chronic hepatitis B and chronic hepatitis C, 1 case each); 11 cases by hypertension; and 4 cases were complicated by type 2 diabetes mellitus. Among the 42 patients, 11 cases had no fever, night sweats or weight loss. 31 cases were accompanied by fever, night sweats and weight loss.Ann Arbor staging: 3 cases had stage I to stage II disease, and 33 cases had stage III to stage IV disease.11 patients had group A symptoms and 31 patients had group B symptoms.The clinical features were depicted in Table 1.

2.2. Treatment regimen

All patients were treated with standard dose-based chemotherapy regimens, including the R-CHOP regimen in 14 cases, the R-DAEPOCH regimen in 24 cases, and the EPOCH regimen in 4 cases. The R-CHOP regimen comprised Rituximab dose of 375 mg/m^2 on the first day of chemotherapy;Doxorubicin 10 mg/m^2, vincristine 1.4 mg/m^2, Cyclophosphamide 750 mg/m^2,intravenous infusion, used on day 2 of chemotherapy; and Prednisone acetate tablets, 100 mg, started on day 2 of chemotherapy and continued for 5 days.The R-DAEPOCH regimen comprised Rituximab at 375 mg/m^2 on the first day of chemotherapy; Doxorubicin 10 mg/m^2, vincristine 0.4 mg/m^2, etoposide 50 mg/m^2, intravenous infusion, starting on the second day of chemotherapy for 4 consecutive days; Cyclophosphamide 750 mg/m^2 on day 5 of chemotherapy; and Prednisone acetate tablets, 100 mg, started on day 2 of chemotherapy and continued for 5 days. The EPOCH protocol comprised Doxorubicin 10 mg/m^2, vincristine 0.4 mg/m^2,etoposide 50 mg/m^2, intravenous infusion, started on the first day of chemotherapy and continued for 4 days; Prednisone acetate tablets 100 mg, starting on day 1 of chemotherapy for 5 consecutive days, and cyclophosphamide 750 mg/m^2,used on day 5 of chemotherapy. All of the above regimens consisted of one chemotherapy cycle every 3 weeks. All patients were additionally treated with a thalidomide regimen. Thalidomide tablets were initially taken orally at 50 mg/night, then increased to 75 mg/night 1 week later, and then taken long-term at 100 mg/ night for more than 6 months after the course of chemotherapy. Patients with CD_4T lymphocyte counts of less than 200/μl were treated with compound sulfamethoxazole for the prevention of pneumocystis yerbii pneumonia. After the first cycle of chemotherapy is over and before the second cycle begins,15 mg of methotrexate, 5 mg of dexamethasone injection and 75 mg of cytarabine for injection were administered intrathecally to prevent central nervous system invasion of lymphoma. Methotrexate, cytarabine, dexamethasone are commonly used in the central nervous system to avoid aggressive lymphoma and leukemia. A phase 2 trial showed that in HIV-associated NHL patients treated with intrathecal injection of cytarabine, the central nervous system recurrence rate was only 3 % [4]. We mainly considered that these patients were all HIV patients with invasive lymphoma, Hence the dosage of cytarabine used was slightly too high, and clinical monitoring had not found central neurotoxicity.Adjustment of ART regimen: TDF+3TC+EFV 27 cases, AZT+3TC+EFV 3 cases, TDF+3TC+LPV/r 3 cases, AZT+3TC+LPV/r 3 cases. During chemotherapy, 23 patients received TDF+3TC+EFV and 19 patients received TDF+3TC+RAL.

Table 1
Basic characteristics of HIV-DLBCL firstly diagnosed in an infectious disease hospital from 2018 to 2020.

	R-CHOP	R-DAEPOCH	EPOCH
HIV-DLBCL	14	24	4
Mean age	49	51	38
Female (example)	3	7	1
Male (example)	11	17	3
CD_4T ≤200/ul	10	18	4
CD_4T >200/ul	4	6	0
Chronic hepatitis B	0	1	0
Chronic hepatitis C	1	0	0
hypertension	3	7	1
Type 2 diabetes	2	2	0
Lymphoma was diagnosed without ART	2	2	0
ART when diagnosing lymphoma	12	22	4
Group A symptoms	2	6	3
Group B symptoms	12	18	1
I/II Phase	1	7	1
III/IV Phase	13	17	3

2.3. Evaluation of clinical efficacy

The evaluation indices were used to assessed complete response, no response, disease progression or recurrence according to the Criteria for Diagnosis and Efficacy of Hematologic Diseases. Overall survival (OS) was defined as time from diagnosis to death or to the end of follow-up. The median follow-up time was 30 months (23–60 months) until January 10, 2023 by consulting medical records and telephone follow-up.

2.4. Evaluation of adverse reactions

Adverse reactions were recorded and evaluated according to WHO criteria for acute and subacute toxic reactions of anticancer drugs, and adverse events were evaluated and graded during each chemotherapy cycle. Infusion-related adverse events, hematological toxicity, liver and kidney toxicity were observed.

3. Results

3.1. Clinical efficacy

All patients received 1 to 8 cycles of chemotherapy. After 4 cycles of chemotherapy, PET-CT scans were performed at 4 weeks and 8 weeks of chemotherapy to determine CR, partial response, and disease progression. A Deaville score of <3 on PET-CT was classified as CR.A total of 5 deaths occurred among the 14 patients treated with R-CHOP at 2-year follow-up (4 deaths in the first year, due to tumor progression. In the second year, 1 case died, the cause of death was combined with other infections), CR occurred in 9 cases (64.2 %). A total of 7 patients who received R-DAEPOCH died at 2-year follow-up (6 died in the first year, and the cause of death was tumor progression), CR occurred in 17 cases (70.8 %); A total of 2 patients (all died within the first year due to tumor progression) and 2 (50 %) patients in the EPOCH protocol died during the 2-year follow-up period.The CR rate of the three groups of chemotherapy regimens was depicted in Table 2. Overall survival was depicted in Table 3.

Table 2
CR rate (%) of chemotherapy regimen in the three groups.

group	Number of cases	CR (%) 1 year	2 year
R-CHOP	14	71.4	64.2
R-DAEPOCH	24	75	70.8
EPOCH	4	50	50

3.2. Adverse reactions

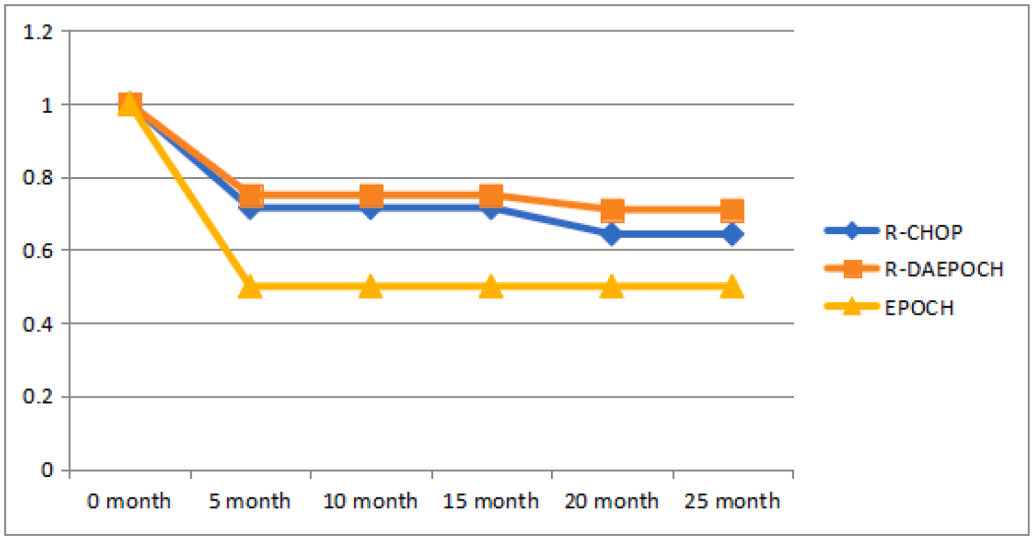
In 2 cases (4.7 %), fever and chills occurred during rituximab infusion. Symptoms disappeared after the suspension of the injection and did not occur again after slowing down the infusion rate. Five patients (11.9%) developed acronumbness, which was considered to be peripheral neuritis caused by chemotherapy drug vincristine. The clinical symptoms improved after nutritional nerve treatment such as mecobalamine was given, so peripheral neuritis caused by thalidomide was not considered. Meanwhile, monitoring showed that no thrombotic events occurred in all patients.Twelve patients (28.5 %) had fatigue, which could be tolerated after symptomatic treatment;Mild renal impairment occurred in 2 cases (4.7 %); Mild liver function impairment occurred in 4 cases (9.4 %). On the 5th day after the second cycle of chemotherapy, 30 patients (71.4 %) began to have different degrees of myelosuppression, including grade II-III myelosuppression in 7 cases, grade IV myelosuppression in 23 cases, and neutrophilia with fever in 20 cases. Digestive tract reactions occurred in 6 cases (14.2%). No acronumbness adverse reactions such as heart damage and venous thrombosis occurred.

4. Discussion

DLBCL has a high incidence and fatality rate, and the best treatment plan has always been the focus of clinical exploration. How to further improve the chemotherapy efficiency and reduce the adverse reactions of DLBCL patients has become an urgent clinical problem. Treatment options for HIV-related hematologic malignancies are abundant in developed, high-income countries, including those requiring high-dose therapy and stem cell transplantation. However, the treatment gap faced by low-income patients in developing countries remains a painful problem. In particular, HIV-DLBCL patients need a cost-effective, safe and effective combination treatment regimens to extend life and improve their quality of life. CHOP was the preferred chemotherapy regimen for DLBCL, and an anti-CD20 monoclonal antibody combined with CHOP has significantly improved the outcome of DLBCL. CHOP has been reported to have a similar effect on HIV-negative and HIV-positive DLBCL patients, with a complete response (CR) rate of 48 %–60 %, while adding R to CHOP increases CR rate by about 10 % [5]. The use of R in HIV-infected patients with lymphoma and CD_4T cell counts less than 50/μl is controversial, but R is still recommended for all DLBCL patients [6]. Studies have found that the R-EPOCH protocol has higher response and survival rates than the R-CHOP protocol [7]. However, there are also studies showing that R-EPOCH and R-CHOP show no statistically significant difference in improving survival rates [8]. Sun et al. [9] followed up 54 cases of patients with HIV-DLBCL, and found that the 2-year overall survival (OS) was 78 % in the dose-adjusted R-EPOCH group and 66 % in the R-CHOP group. In addition, there was a higher incidence of CNS involvement in HIV-DLBCL patients than in HIV-negative patients with DLBCL [10]. There are no controlled studies on the role of CNS prevention and the optimal strategy for HIV-DLBCL. Consequently indications for CNS prophylaxis (intrathecal injection of methotrexate, dexamethasone, cytarabine) can be followed in HIV-negative populations.All patients underwent CNS prophylaxis for 1–6 times without any CNS involvement, which may be one of the treatment methods for patients to achieve good survival.

ART is an essential link in the treatment of HIV-DLBCL. ART can not only prevent the reduction of CD_4T cells, but also reduce the number of HIV viruses. However, if ART is stopped during chemotherapy, it will take about 1 year for CD_4T cells to recover to the baseline level [11]. The guidelines of the National Comprehensive Cancer Network of the United States suggest that ART should be started as soon as possible at the beginning of tumor therapy for HIV patients with tumor complications [12]. ART drugs can be used safely during chemotherapy, but enhancers (Ritonavir and biestat,etc.) increase the toxicity of vincristine and other chemotherapy drugs. Zidovudine can cause myelosuppression, and should be avoided in combination with chemotherapy drugs that may cause myelosuppression. Further, routine blood monitoring should be strengthened [13,14]. As a result,during the treatment of lymphoma, appropriate ART regimens can be selected according to drug interactions or overlapping toxicity of chemotherapy drugs. Integrase inhibitors have a low incidence of adverse reactions and few interactions between drugs, hence it is recommended for antiviral therapy to be based on nucleoside and integrase inhibitors, so as to minimize the interaction with

Table 3
Overall survival of the three groups.



chemotherapy regimens. Retrospective analysis was conducted on 42 patients newly diagnosed with HIV-DLBCL in our hospital, most of whom were from remote areas, with underdeveloped economies and low income. Only 19 patients used an integrase inhibitor ART regimen, and 23 patients used EFV therapy regimen.At the same time, 4 patients could not afford R cost and were treated with EPOCH scheme. During the monitoring period, CD_4T cell counts showed no significant change compared with that before chemotherapy. If there is a next step, it should be to consider adding HIV-RNA monitoring to understand the efficacy of antiviral therapy. Chemotherapy will damage the immune function of patients, tumor cells are more likely to proliferate, multiply, infiltrate and metastasize. Lenalidomide has been recommended by the NCCN guidelines as the first-line maintenance therapy for DLBCL. However, its use is limited by its high price, while thalidomide has been proven to have anti-tumor effects in vivo and in vitro experiments in animals, and the prognosis and efficacy of patients on combined treatment with chemotherapy are more ideal [15,16]. It was found that thalidomide could inhibit the angiogenesis by inhibiting cyclooxygenase-2 (COX-2) and down-regulating the expression of prostaglandin E2(PGE2). It can also inhibit the expression of transcription factor NF-KB, and inhibit the occurrence and progression of lymphatic system tumors [17,18]. In addition, thalidomide can induce sedation, antiemetic and hypnotic effects through its self-carried piperidine ring structure, thereby reducing chemotherapy-related gastrointestinal reactions and significantly improving chemotherapy tolerance in DLBCL patients [19]. At the same time, the drug is inexpensive and patients can maintain treatment for a long time, which helps the recovery and prognosis of low-income patients. Although one of the common side effects of thalidomide is to cause peripheral nerve symptoms and thrombosis, the incidence of peripheral nerve symptoms and thrombosis did not increase significantly in the patients in this group, which may be related to the total dose of the drug (usually occurs at 40–50 g), and has nothing to do with the course of treatment and daily dose. Moreover, the drug is cheap, and patients can it as take long-term maintenance therapy. This helps the recovery and prognosis of low-income patients. Immunosuppression caused by HIV infection will increase the risk of opportunistic infections, and myelosuppression caused by chemotherapy will further increase this risk of opportunistic infection. preventive anti-infection measures are very important in the treatment of HIV-DLBCL. Further, the use of compound sulfamethoxazole to prevent pneumocystis yerbii pneumonia is recommended. The use of compound sulfamethoxazole also reduces the incidence of toxoplasmosis. During chemotherapy, all patients in the 3 groups had different degrees of myelosuppression, most of which occurred about 1 week after the end of chemotherapy, mainly agranulocytosis, anemia and thrombocytopenia. Through active intervention, including the use of granulocyte stimulating factor, anti-biotics, red blood cell infusions and platelet infusion therapy, no patients died from these complications of chemotherapy drugs.

Through the retrospective analysis of this group,combined treatment with thalidomide was effective in HIV-DLBCL patients.The combination regimen may be an effective choice for low-income HIV-DLBCL patients in remote areas. Due to the limited conditions of our institution, we failed to compare treatment programs with those of other non-HIV infected patient. At the same time, the follow-up time of patients was short and the funds were limited, so we failed to conduct HIV-RNA monitoring. In the future, it is necessary to conduct studies with a larger sample size, longer follow-up time, and introduce new targeted drugs to explore effective treatment programs for low-income HIV-DLBCL patients.

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Informed Consent Statement

Written informed consent from patients can be obtained to publish this article.

Data availability statement

Due to ethical and privacy concerns, data supporting this study is not publicly available and may be obtained from the first or corresponding author upon reasonable request.

Contract of benefit

The author states that there is no contract of benefit.

CRediT authorship contribution statement

Peng fei Tao: Writing – review & editing, Writing – original draft, Resources, Methodology. **Chuan Qian:** Data curation. **Qi wen zhou:** Data curation. **Sen Lin:** Methodology, Data curation. **Dan qing Wang:** Methodology, Data curation. **Xi Wang:** Methodology, Data curation. **Shi fen Chen:** Methodology, Data curation. **Hai yan Min:** Writing – review & editing, Project administration.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

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