

Analysis of the effect of R-CHOP regimen of pegylated liposomal doxorubicin on elderly patients with stage III-IV diffuse large B-cell lymphoma

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Abstract: To explore the effect of R-CHOP regimen of pegylated liposomal doxorubicin (PLD) on elderly stage III-IV diffuse large B-cell lymphoma (DLBCL). A retrospective analysis was conducted on the treatment information 80 elderly cases of stage III-IV DLBCL admitted to our hospital from April 2017 to April 2020. According to treatment methods, they were divided into experimental groups (40 cases, using R-CHOP with PLD) and controls group (40 cases, using the traditional R-CHOP regimen). We compared the treatment effect, survival rate, cardiotoxicity and adverse reactions of the patients. (1) The short-term degree of effectiveness treatment in the experimental group was 85%, which was not significantly different from 80% in other patients ($p>0.05$). (2) 2-year OS or PFS of experimental group were better more ($p<0.01$) and the treatment advantage of the experimental group increased with time. (3) Incidence of neutropenia and alopecia in experimental group was lower more ($p<0.05$). (4) Cardiotoxicity indexes of experimental group were lower ($p<0.05$). The PLD-containing R-CHOP regimen can improve the long-term inventory level elderly cases of stage III-IV DLBCL, reduce the incidence of grade IV neutropenia and alopecia, alleviate the cardiotoxicity caused by chemotherapy, and have better safety.

Keywords: Polyethylene glycol liposomal doxorubicin, R-CHOP regimen, diffuse large B-cell lymphoma, elderly patients with stage III to IV, analysis of efficacy.

DLBCL belongs to category of lymphoma and is most common type of non-Hodgkin's lymphoma. Clinical data shows that DLBCL accounts for more than 40% of malignant lymphomas in China, and it occurs mostly in middle-aged and elderly people, among which 50-70 years old is the peak age (Shen *et al.*, 2018; Takahashi *et al.*, 2017). With the constant increase of the elderly population in China, the incidence of DLBCL is on the rise over years. Rituximab cyclophosphamide, hydroxydaunorubicin, Oncovin and R-CHOP are also under study the first-line standard regimen for the clinical treatment of DLBCL. However, the doxorubicin used in the traditional R-CHOP regimen can cause severe cardiotoxicity such as myocarditis and arrhythmia (Liu *et al.*, 2019; Araie *et al.*, 2017). Since most elderly patients with DLBCL have a decline in organ function and are accompanied by cardiovascular diseases, they have poor tolerance with chemotherapy, which causes more severe cardiotoxicity and affects the therapeutic effect. PLD is a liposome preparation that can encapsulate doxorubicin in liposomes, protect it from being recognized by the mononuclear macrophage system, and prolong its time in blood circulation (Fan *et al.*, 2017). Compared with doxorubicin, PLD has less myocardial distribution and lower peak concentration of myocardial drugs, which can effectively reduce cardiotoxicity and improve the treatment safety of elderly DLBCL patients. As the application of PLD in chemotherapy for elderly DLBCL patients grows, its clinical efficacy has gained increasing

attention (Kuhnl *et al.*, 2017). To explore the effect of the PLD-containing R-CHOP regimen in treatment in elderly DLBCL cases with stage III to IV, implement in-depth analysis on 80 elderly DLBCL cases with stage III to IV admitted to our hospital over a period of April 2017 to April 2020.

MATERIALS AND METHODS

General information

We retrospectively analyzed the clinical data 80 elderly cases has stage III-IV DLBCL admitted to local hospital between April 2017 and April 2020. They were divided of experimental group and control group because of treatment method, each group 40 patients. No obviously differences was detected between patients in clinical data with respects to age and disease types ($p>0.05$). The details are shown in table 1.

Inclusion/exclusion criteria

Inclusion criteria

- (1) Newly-treated patients with DLBCL stage III to IV diagnosed by pathology;
- (2) Age ≥ 60 years old, normal intelligence and cognition;
- (3) Tumor lesions can be measured objectively, and the life expectancy exceeds 3 months;
- (4) The study was conducted with the permission of the hospital ethics committee and all patients had informed consent.

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Exclusion criteria

- (1) Acquired immunodeficiency syndrome, severe heart, liver and kidney dysfunction;
- (2) Unstable myocardial infarction or other clinically active heart diseases prior enrollment;
- (3) Contraindications to corticosteroids, only unmeasurable tumor lesions;
- (4) Involuntarily participate in the research, or withdraw from the research halfway.

Methods

(1) The experimental group used the R-CHOP regimen containing PLD, and the drug dosage and usage were as follows. Day 0: Rituximab (produced by Shenzhen Feisi Biotechnology Co., Ltd.) 375mg/m² was given intravenously (IV) (Zhang *et al.*, 2019). Day 1: Vincristine (produced by Sichuan Weikeqi Biotechnology Co., Ltd.) 1.4 mg/m² was given IV. Day 1: PLD (produced by Shanghai Zhangjiang Biomedicine Co., Ltd.) 30mg/m² was given IV (Kanemasa *et al.*, 2017; Wang *et al.*, 2020). Day 1: Cyclophosphamide (produced by Shanghai Maclean Biochemical Technology Co., Ltd.) 750 mg/m² was given IV. Day 1-5: Prednisone (produced by Hubei Huizepu Pharmaceutical Technology Co., Ltd.) 100 mg/m², was given orally once a day (Maude *et al.*, 2014).

(2) The control group used the traditional R-CHOP regimen. Except doxorubicin (Shanghai Yuanye Biotechnology Co., Ltd.) 50mg/m² IV was given on day 1, the dosage and usage of the rest of the drugs were the same as the experimental group. Take medication every 21 days. The treatment was mainly implemented in 2005 less than 6 cycles (Prusila *et al.*, 2019).

Efficacy evaluation

The therapeutic effect of all patients was evaluated because of evaluation standard of the World Health Organization for solid tumors, and coded As Cr, PR, SD and PD, ORR. $ORR = (CR+PR)/n \times 100\%$. CT scan of the chest, neck, abdomen and pelvis and color Doppler ultrasonography of superficial lymph nodes are performed every 2 cycles of chemotherapy. If the patient exhibit symptoms of bone marrow invasion, bone marrow cytology is required. Those whose curative effect is evaluated as CR or PR can continue chemotherapy. Within 2 years upon the completion of treatment, follow-up will be conducted every 3 months, and after 2 years, follow-up will be conducted every 6 months.

Adverse reactions evaluation

Toxicity was graded based on the standard stipulated by the National Cancer Institute, the adverse reactions in the two groups of patients were recorded. Blood routine, 12-lead electrocardiogram and serum troponin T test were performed before and after each cycle of administration. Left ventricular function measurement and cardiac color Doppler ultrasound were performed before chemotherapy and every 2 cycles after chemotherapy.

STATISTICAL ANALYSIS

The statistical software SPSS21.0 was used in our study. The count data are displayed in the form of [n (%)] and X² test was performed for the comparison. The survival rate was analyzed by Kaplan Meier method, and the difference between survival groups was shown in the form of number rank. The difference was assumed at $p < 0.05$.

RESULTS

Comparison of short-term efficacy between the two groups

The effective rate of short-term treatment in the experimental group was 85%, while it was 80% in one group. No significant difference was identified ($p > 0.05$, table 2).

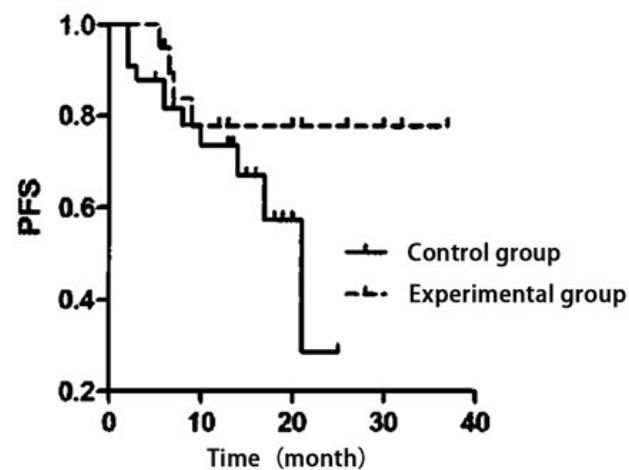


Fig. 1: Long-term survival rate PFS analysis of two groups of patients

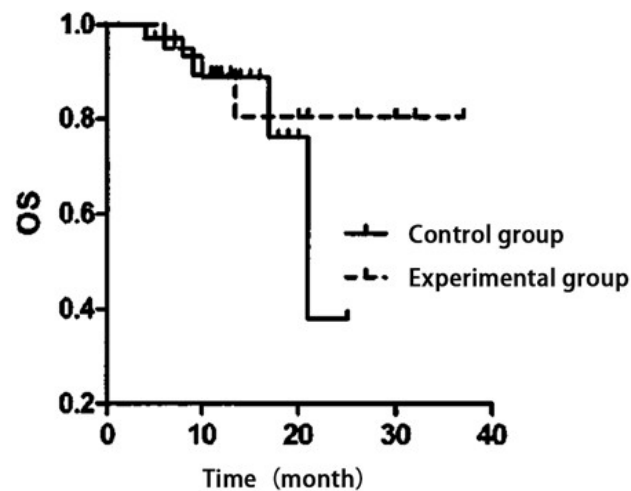


Fig. 2: Long-term survival rate OS analysis of the two groups of patients

Table 1: Comparison of general information of the two groups of patients

Indexes	Experimental group (n=40)	Control group (n=40)	χ^2	P
Age [year (%)]	-	-	-	-
60-69	21	23	0.239	0.887
70-79	14	13		
80以上	5	4		
Sex [n (%)]	-	-	-	-
Male	23	22	0.051	0.822
Female	17	18		
ECOC score [n (%)]	-	-	-	-
0	10	9	0.325	0.955
1	15	16		
2	12	13		
3	3	2		
Ann arbor stage [n (%)]	-	-	-	-
II	9	10	0.144	0.931
III	25	25		
IV	6	5		
aaIPI grade [n(%)]	-	-	-	-
2	22	23	0.016	0.899

Table 2: Comparison of short-term curative effect between the two groups of patients [n(%)]

Groups	N	CR	PR	SD	PD	ORR
Experimental group	40	28(70.0)	6(15.0)	2(5.0)	4(10.0)	34(85.0)
Control group	40	26(65.0)	6(15.0)	2(5.0)	6(15.0)	32(80.0)
χ^2						0.346
P						0.556

Table 3: Comparison of adverse reactions between the two groups of patients [n(%)]

Adverse reactions	Experimental group (n=40)	Control group (n=40)	χ^2	P
alopecia	6(15.0)	18(45.0)	8.571	0.003
IV Mesgranulocytopenia	2(5.0)	14(35.0)	11.250	0.001
thrombocytopenia	9(22.5)	7(17.5)	0.313	0.576
Hand-foot syndrome	7(17.5)	2(5.0)	3.130	0.077
Anemia	6(15.0)	8(20.0)	0.346	0.556
Neurotoxicity	4(10.0)	2(5.0)	0.721	0.396
Hepatic dysfunction	7(17.5)	12(30.0)	1.726	0.189
Renal insufficiency	2(5.0)	3(7.5)	0.213	0.644
Gastrointestinal reaction	12(30.0)	11(27.5)	0.061	0.805
Stomatitis	4(10.0)	3(7.5)	0.157	0.692

Table 4: Comparison of cardiotoxicity between the two groups [n(%)]

Indexes	Experimental group (n=40)	Control group (n=40)	χ^2	P
Myocardial infraction	1(2.5)	6(15.0)	3.914	0.048
Myocardial damage	0(0.0)	5(12.5)	5.333	0.021
Electrocardiographic abnormality	3	10	4.501	0.034
ST-T change	1(2.5)	5(12.5)		
Atrioventricular block	1(2.5)	0(0.0)		
Paroxysmal atrial tachycardia	1(2.5)	2(5.0)		
Atrial premature beat	0(0.0)	3(7.5)		
Cardiac insufficiency	0	4	4.211	0.040
I-II grade	0(0.0)	2(5.0)		
III-IV grade	0(0.0)	2(5.0)		

Comparison of long-term survival rates between the two groups

One-year OS and PFS did not differ significantly between all groups ($p>0.05$), but 2-year OS and PFS of experimental group were better than those of another group ($p<0.01$) and treatment advantage of experimental group increased with time extended (fig. 1 and fig. 2).

Comparison of adverse reactions between the two groups of patients

The number of neutrophils decreased and the probability of hair loss was lower in the experimental group ($p < 0.05$), there no difference was noticed in other adverse reactions ($p>0.05$). See table 3.

Comparison of cardiotoxicity between the two groups

Cardiotoxicity indicators (myocardial infarction, myocardial damage, abnormal electrocardiogram, and cardiac insufficiency) in the experimental group were lower ($p<0.05$). See table 4.

DISCUSSION

DLBCL is a malignant disease originating from the lymphatic system. The main clinical manifestations are rapid lymph node enlargement and progressive weight loss. It is highly invasive and disseminated (Hertzberg *et al.*, 2017; Zhou *et al.*, 2020). DLBCL mostly occurs in middle-aged and elderly people aged 50-70. Most of these patients have decline in body function and are often accompanied by underlying diseases. The current first-line treatment for DLBCL-R-CHOP is subject to the cardiotoxicity of Adriamycin, which is poorly performed in elderly patients (Lastra-German *et al.*, 2019; Wohnner *et al.*, 2017). It is urgent and a hot spot in clinical research to find an efficient and low-toxicity chemotherapy regimen for DLBCL in recent years.

PLD is a new type of doxorubicin, which can effectively inhibit tumor metastasis and growth, and improve tumor treatment effect. A study in Italy showed that the CR of the R-CHOP regimen with PLD instead of doxorubicin in elderly DLBCL was 59% and the ORR was 76%, and no obviously difference in cardiotoxicity between cases before and after treatment ($p>0.05$) (Jeong *et al.*, 2017; Tanimura *et al.*, 2018; Park *et al.*, 2019). This suggests that the PLD-containing R-CHOP regimen is not only effective, but also less cardiotoxic, and it is a safer treatment regimen for elderly DLBCL.

This study found that recent treatment effective rate of experimental group was 85%, which was not significantly different from 80% of the control group ($p>0.05$). This is in line with the study (Fu *et al.*, 2014), in which 64 cases of elderly DLBCL were divided into PLD-containing R-CHOP group and traditional R-CHOP group according to the treatment plan, with 32 cases in each group. The result found that after 6 cycles chemotherapy, there no

difference of effective rate of short-term treatment between all groups (81.25% VS 71.88%, $p>0.05$). This suggests that the short-term treatment effect of the PLD-containing R-CHOP regimen is similar to the traditional R-CHOP regimen.

The study also found that no marked difference was noticed in OS and PFS of all groups within one year of treatment ($p<0.05$), but the two-year OS and PFS of experimental group were better than those of another group ($p<0.01$), and advantages of this group become more prominent over time. This suggests that compared with the traditional R-CHOP program, the PLD-containing R-CHOP program has a stronger long-term treatment advantage. Additionally, the study found that probability of a small number of neutrophils and alopecia in experimental group was lower ($p<0.05$). And cardiotoxicity indexes of experimental group were lower ($p<0.05$). This is similar to the results of the study by Cohen *et al.* (Cohen *et al.*, 2019), where 80 patients with multiple myeloma were divided of POM group (40 patients, POM treatment) and PLD group (40 patients, PLD treatment), and found incidence of neutropenia and cardiotoxicity in PLD group were lower than those in POM group (all $p<0.05$). This suggests that PLD can reduce cardiotoxicity in patients and reduce the occurrence of alopecia and neutropenia.

CONCLUSION

In conclusion, compared with the traditional R-CHOP regimen, the PLD-containing R-CHOP regimen can improve the long-term survival probability elderly cases with stage III-IV DLBCL, reduce the incidence of grade IV neutropenia and alopecia and relieve chemotherapy-induced cardiotoxicity with higher safety.

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