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Evaluation of the R-CHOP Treatments Compared with CHOP on Non-Hodgkin Malignant Lymphoma Patients with Big Cell Spread with CD 20 (+) at Thai Nguyen Cancer Center Oncology

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Abstract In this study, we have evaluated the R-CHOP regimens compared with CHOP in non-Hodgkin malignant lymphoma patients with spreading large cells with CD 20 (+) at Thai Nguyen Cancer Center from 2013 to 2018. A total of 85 patients were analysed by diagnosing the non-Hodgkin malignant lymphoma (ULAKH), in which the 45 patients were treated with R-CHOP regimens and 40 patients were with CHOP regimens. The average age at diagnosis of the patients was 46. The highest age at 50-59 years old accounted for 51% of group A and 50% in group B; the age group ≥ 70 accounts for a low rate of 6.7% of group A and 7.5% of group B. Stage IV accounts for the highest rate of 40.0% in both groups, followed by stage III, accounting for 31,1% of group A and 32.5% of group B, phase II accounted for 28.9% of group A and 27.5% of group B. The disease met completely accounted for a high rate of 80.0% in group A and 65% in group B. Partial response accounted for 17.8% of group A and 27.5% of group B. Progressive disease met 01 patient in group B. The main toxicity of the regimen on red blood cell formation level I is 64.4% of group A; 57.5% of group B. Leukopenia Grade I was 71.1% of group A and 65.6% of group B. Kaplan - Meier 5-year survival period in stage II was higher than 85%, stage III was 65%; stage IV 45%. Full 5-years survival for ULAKH with CD 20 (+) for R- CHOP 84%; CHOP was 65% difference was statistically significant with p <0.001. Duration of disease-free survival after 5 years of patients treated with R-CHOP was 72.5%, CHOP was 51.5%, the difference was statistically significant with p <0.05. The R-CHOP was increased the rate of complete response was high than the CHOP was complete response and this difference was evident when monitoring the overall survival time after 5 years of patients on R- CHOP was 19% higher than CHOP and the 5-year non-disease survival period of patients treated with R-CHOP (72.5%) was higher than that of CHOP alone (51.5%).

Keywords Malignant lymphoma non- Hodgkin; R-CHOP; CHOP

1. Introduction

Malignant lymphoma non- Hodgkin is a group of malignant lymphocyte proliferation with complex and different clinical manifestations, histopathology, prognosis and treatment. The disease occurs in all countries around the world but the incidence is higher in developed and developing countries. In the US, it is estimated that in 2010 there were 65,980 new cases and about 19,000 deaths from this disease and ranked fifth in all types of cancer. In Vietnam, the age-standardized rate is 5.2 / 100,000 ranked 7th in all types of cancer. Non-Hodgkin malignant lymphoma type B accounts for about two-thirds of cases. Non-Hodgkin's malignant lymphoma is a rather complex disease with many risk factors and related mechanisms. The classic prognostic factors are based on Age, blood LDH index, disease stage, Hemoglobin blood index and a number of lymph node lesions. Non-Hodgkin's malignant Ulym-based treatment method based on two main criteria for determining treatment strategy is based on the diagnosis of histopathology and the classification of disease stage, the presence of

syndrome B should also be weighed consider. The general direction for the treatment of non-Hodgkin malignant lymphoma is a multimodal combination and mainly chemotherapy - combined radiation therapy. Non-Hodgkin's malignant lymphoma usually manifests itself in widespread condition, even if the disease progresses even during radiation therapy. Therefore chemotherapy is usually applied to most patients. Select chemotherapy regimens based on factors such as histopathology, stage of the disease, with or without syndrome B, overall index and combination diseases. Today with the advancement of science and technology the target treatment for cancer patients in general and non-Hodgkin's malignant lymphoma, in particular, has brought good results for patients. Chemotherapy combined with monoclonal antibodies is the initial treatment choice for large cell lymphomas, but many patients for many reasons are not adequately and adequately treated. The Thai Nguyen Oncology Center receives patients with non-Hodgkin's malignant lymphoma that spreads over 80%, affecting the results of treatment. To evaluate the treatment results and the additional survival time after treatment between R-CHOP and CHOP regimens, we study this topic with the goal: Evaluating the results of R-CHOP regimens compared with CHOP in non- Hodgkin malignant lymphoma patients with spreading large cells with CD 20 (+) at Thai Nguyen Center Oncology from 2013 – 2018.

Materials and Methods

Patients

Including 85 non - Hodgkin malignant lymphoma patients with spreading large cells with CD 20 (+) treated at Thai Nguyen Oncology Center, of which 45 patients were treated with R-CHOP and 40 patients were treatment of CHOP from January 1/ 2013 to October 30/ 2018 at Thai Nguyen oncology Center.- Thai Nguyen Central Hospital.

Methods

Select patients to study

Criteria for selecting research groups: Patients with a definitive diagnosis by histopathology are non-Hodgkin malignant lymphoma (gold standard) as the following:

- Age 18 - 70
- The patient was diagnosed with malignant lymphoma without Hodgkin
- Diagnosis of histopathology is malignant lymphoma not Hodgkin spread large cells
- Have a CD 20 test
- ECOG index 0 - 3
- No second cancer
- Not treated with previous chemicals
- Patients with indications for chemical transfer
- The patient does not suffer from severe acute and chronic diseases that are at risk of death within 6 months, without any other cancer.
- Patients have fully explained the treatment course, voluntarily participated in the study and completed the treatment course.
- Treatment of 6-8 rounds of R-CHOP regimen; CHOP
- Have a full record

Patients are given regular follow-up visits or have answers from patients and families by phone or mail

Exclusion criteria for the research team

- Histopathology is not a malignant U lymphoma without Hodgkin.
- Being suffering from severe combination of diseases.
- Refuse to participate in research or abort treatment.
- Poor response, no response or progression after chemotherapy 3-4 time

General criteria

The age, gender, career, time

Clinical criteria

- Symptoms of the disease
- Functional symptoms: tumour palpation, lymph nodes ... ..
- Symptoms of entity: tumours, lymph nodes; location, size, nature, density ...
- M: metastasis ...
- Systemic symptoms: ECOG index, weight loss, fever
- Other symptoms

Subclinical

Image diagnosis methods: Normal X-ray, CT scan, abdominal ultrasound: conducted before treatment to assess the stage of the disease and after each course of treatment and re-evaluate the overall after 4 cycles and 8 treatment cycles as the following:

+ Determining position, size, lymph nodes
+ Determine position, size, metastasis
+ Determine metastasis.
- Diagnosis of histopathology
+ U biopsy, diagnosis of malignant lymphoma histopathology without Hodgkin
- Histopathology: histopathological categories classified by WHO in 2001
+ CD 20 test
- Other tests
- Substance indicating tumour points: B2 microglobulin, LDH
- Peripheral blood test: the number of erythrocytes, hemoglobin and the number of white blood cells, platelets before each chemotherapy session.
- Bone marrow: assessing the development of bone marrow, invading cancer cells into the marrow
- Indicators for evaluating liver and kidney function ...

* Evaluate the stage of disease according to the Ann Arbor system
- Conduct chemotherapy for patients
- Evaluate treatment results

Procedures

After the patients were diagnosed with non-Hodgkin's malignant lymphoma spreading large cells with CD 20 (+), all the above criteria were treated with R-CHOP regimen (Group A). For patients without R-CHOP treatment conditions, treatment of CHOP regimens (group B) is indicated as below:

Cyclophosphamid: 750mg/m2 –TM – 1 day;
Doxorubicin: 50mg/m2 –TM – 1 day;
Vincristin: 1,4mg/m2 –TM – 1 day;
Prednisolon: 100mg/2 – PO - From 1 to 5 days after a meal
Rituximab CD20(+): 375 mg/m2 - 375 mg/m2 – day 1
Duration: 21 days x 6 -8 cycles

Other support drugs

After each course of treatment, patients will be re-examined for clinical, subclinical assessment, response to treatment to be able to adjust the dose accordingly. All patients in the study after 3- 4 episodes were assessed for response if the patient responded to the next 3 to 4 treatments.

Management of situations encountered during treatment: leukocytosis, infection, increased liver enzymes, increased creatinine will be managed promptly and only transfer the chemical when the indicators return to the allowable level.

Evaluate the treatment effects and follow-up side effects

Time of evaluation: Before and after each treatment session, after 3-4 times and 6-8 general evaluation.

Based on clinical and subclinical information: Systemic status, clinical symptoms, laboratory tests compared with pre-treatment information.
Evaluation of chemical treatment response: Based on WHO standards.
Evaluation of side effects: toxicity analysis based on WHO standards.
Follow:
- All patients were followed up for at least 6 months after the end of the treatment course.
- Monitor response immediately after the end of the treatment course and from 2 to 3 months by clinical examination, image diagnosis...
- Track extra lives and quality of life: by mail or phone

Method of evaluating research criteria
- Evaluate WHO treatment response by clinical, imaging diagnosis before, during and after treatment.
- Evaluation criteria: Overall assessment according to ECOG; evaluation of the stage of disease according to Ann - Arborr
- Evaluate treatment: Evaluate the results at the end of treatment; evaluate with chemical treatment response according to WHO standards. Assessment of toxicity of the regimen according to the standards of the World Health Organization in 2000 on the classification of toxicity of anticancer drugs
- Outcome: assess the overall survival time after 6 months, 12 months, 24 months; 36 months; 48 months and 60 months according to Kaplan-Meier.
- Based on the results of re-examination and direct examination of patients.
- Send a letter of exploration about the lifetime and the condition of the patient who is alive or dead.
- Disease recurrence in the area, in the region, distant metastasis.
- The extra life is determined based on the hospital admission date, the last date of the information, the patient's death date
Through additional time tracking, learn some factors related to lifetime such as:
+ Age; Disease stage; Histopathology; CD20 index ...-

Methods of data collection
Collect data according to unified research form

Statistical analyses
Research results are processed according to the medical statistical method on SPSS 20.0 software.

Ethical issues in research
The study was conducted with the willingness of patients to participate.
Treatment regimen has been agreed according to the standards of the Ministry of Health
The patient's information and research data are kept confidential.

Results and Discussion
Clinical and subclinical characteristics of patients
The age group of 50-59 accounts for the highest percentage of 51% of group A and 50% of group B; age group ≥ 70 accounts for a low rate of 6.7% of group A and 7.5% of group B as shown in Table 1. According to many studies, the average age of ULAKH at the time of diagnosis is 55 years, the age group infected is 30-40 and 50-60 [1]. In our study, the average age at the time of diagnosis was 46. The highest age was 50-59 years old, accounting for 51% of group A and 50% in group B; age group ≥ 70 accounts for a low rate of 6.7% of group A and 7.5% of group B. The number of patients with major clinical manifestations before being admitted is 95.5%. The number of authors announced that non-Hodgkin malignant lymphoma manifested mainly in lymph nodes. Our research results are similar to some authors.

Table 1: Distribution of non-Hodgkin malignant lymphoma by age

Ages	Group A		Group B	
	Cases	Ratio	Cases	Ratio
30- 39	3	6.7	2	5.0
40-49	7	15.6	5	12.5
50-59	23	51.0	20	50.0
60-69	9	20.0	10	25.0
≥70	3	6.7	3	7.5
Total	45	100	40	100

In the position of the left ganglion group accounted for the highest proportion of 31.1% of group A and 30.0% of group B. The size of lymphadenopathy greater than 5 cm accounted for the highest proportion of 84.4% of group A and 82.3% of group B. The number of lymph node lesions in 4 regions accounted for the highest proportion of 53.4% of group A and 55.0% of group B as presented in Table 2. In the position of the left ganglion group accounted for the highest proportion of 31.1% of group A and 30.0% of group B, lymph nodes in other groups and positions with a lower rate. This is also the position of the lymph nodes that are damaged in accordance with the disease phase. The size of lymph nodes greater than 5 cm accounts for the highest proportion of 84.4% of group A and 82.3% of group B. The number of lymph node lesions in 4 regions accounts for the highest proportion of 53.4% of group A and 55.0% of group B. This result is higher than the results of some foreign authors, which suggests that our patients often come to the hospital late.

Table 2: Location, size, properties of tumours, lymph

Characteristics of Tumor and lymph nodes	Group A		Group B	
Location Nodes	**Cases**	**Ratio**	**Cases**	**Ratio**
Group the right neck	10	22.2	9	22.5
Group the left neck	14	31.1	12	30.0
Right armpit	5	11.1	5	12.5
Left armpit	8	17.8	8	20.5
Right groin	3	6.7	3	7.0
Left groin	3	6.7	2	5.0
Agency outside the ganglion	2	4.4	1	2.5
Total	45	100	40	100
Size of tumours, lymph nodes				
< 2cm	2	4.5	2	4.6
2-5 cm	5	11.1	5	13.1
> 5 cm	38	84.4	33	82.3
Total	45	100	40	100
Number of lymph node lesions				
1	2	4.4	2	5.0
2	8	17.8	7	17.5
3	11	24.4	9	22.5
4	24	53.4	22	55.0
Total	45	100	40	100

Stage IV accounted for the highest rate of 40.0% in both groups, followed by Stage III, accounting for 31.1% of Group A and 32.5% of Group B, Stage II accounted for 28.9% group A and 27.5% of group B as presented in Table 3. Stage IV accounted for the highest rate of 40.0% in both groups, followed by Phase III, accounting for 31.1% of group A and 32.5% of group B, phase II accounted for 28.9% of group A and 27.5% of group B. this indicates that the number of patients coming to the hospital in the late stage accounts for a high percentage.

Table 3: Clinical stages

Stages	Group A		Group B	
	Cases	Ratio	Case	Ratio
Stage II	13	28.9	11	27.5
Stage III	14	31.1	13	32.5
Stage IV	18	40.0	16	40.0
Total	45	100	40	100

The response completely accounted for a high rate of 80.0% in group A and 65% in group B. Partial response accounted for 17.8% of group A and 27.5% of group B. Progressive disease meet 01 patient in group B as shown in Table 4.

Table 4: Response after the end of treatment

Response	Group A		Group B	
	n	Ratio	n	Ratio
Completely	36	80.0	26	65.0
A part	8	17.8	11	27.5
The disease remains the same	1	2.2	2	5.0
The disease progresses	0	0	1	2.5
Total	45	100	40	100

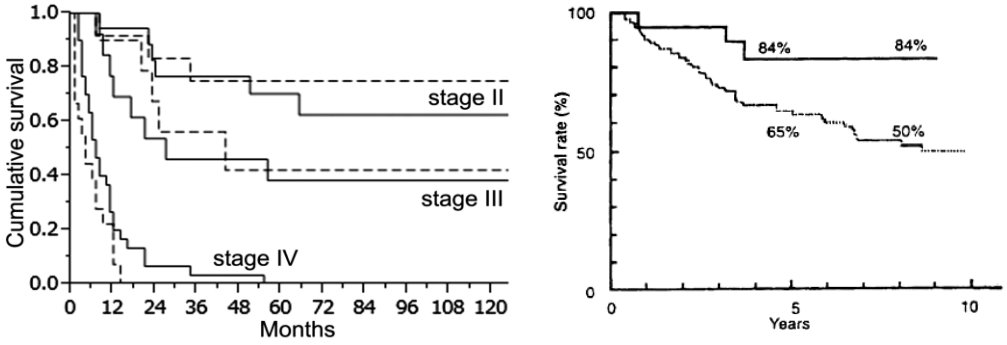
The toxicity of the primary red blood cell regimen of level I is 64.4% of group A; 57.5% of group B. Leukopenia Grade I was 71.1% of group A and 65.6% of group B. degree 2 was17.8% of group A and 23.6% of group B as shown in Table 5. Completely responsive disease accounted for a high rate of 80.0% in group A and 65% in group B. Partial response accounted for 17.8% of group A and 27.5% of group B. Disease progress was met with one patient in group B. According to many studies, it was found that the proportion of patients who recovered from treatment with R-CHOP regimen was very high. In previous years, there was no target treatment drug, the rate of patients responding completely low, the disease met a high part. This result is also consistent with the results of domestic and foreign authors. During the follow-up of the results after re-examination, the patient did not see any relapse and metastasis. This suggests that the treatment regimen for R-CHOP in non-Hodgkin's lymphoma has CD 20 (+) that the rate of response and cure is higher than that of CHOP regimens. The toxicity of the primary hemoglobin regimen of hemoglobin level I was 64.4% in group A; 57.5% of group B. Leukopenia Grade I 71.1% of group A and 65.6% of group B. degree 2 17.8% of group A and 23.6% of group B. This indicates treatment regimens R - CHOP and CHOP have nearly equal rate of haematopoietic lesions.

Table 5. Toxicity of the regimen on the hematopoietic: cases (C); Ratio (R) (C = 45); (C=40)

Organ	Group A								Group B							
	Degree 1		Degree 2		Degree 3		Degree 4		Degree 1		Degree 2		Degree 3		Degree 4	
	C	R	C	R	C	R	C	R	S	R	C	R	C	R	C	R
Red blood cells	29	64.4	11	24.4	3	6.7	2	4.5	23	57.5	12	30.0	3	7.5	2	5.0
White blood cells	32	71.1	8	17.8	3	6.7	2	4.4	26	65.6	9	23.6	3	7.6	2	5.0
Hb	36	80.0	2	4.4	5	11.2	2	4.4	30	75.0	4	10.0	5	12.5	1	2.5
Platelet	35	77.7	4	8.9	3	6.7	3	6.7	30	75.0	3	7.5	4	10.0	3	7.5

Evaluate the extra life according to Kaplan – Meier

The 5-year life survival of Stage II is higher than 85%, Stage III is 65%; stage IV 45%. The 5-year overall life expectancy for ULAKH with CD 20 (+) for R-regimen treatment - CHOP 84%; CHOP regimen 65% difference was statistically significant with p <0.001 (Figure 1).



A B

Figure 1:A: Extra life according to the stage of disease; B: Total lifetime

The disease-free life after 5 years of patients treated with R-CHOP regimen 72.5%, CHOP regimen 51.5%, the difference has statistical significance with p <0 (Figure 2).

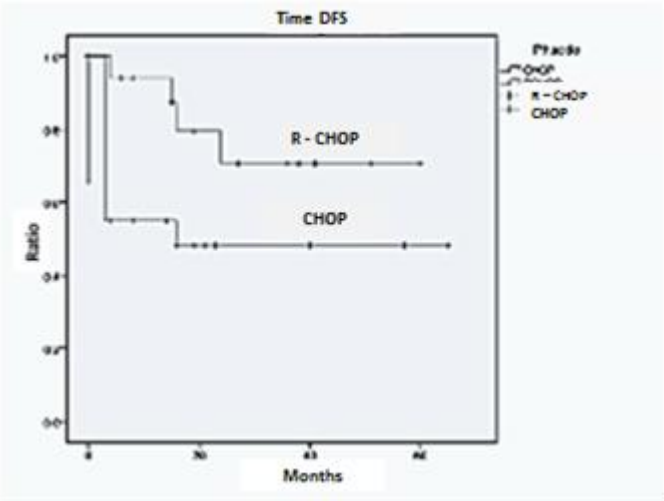


Figure 2. The survival life is not sick

Kaplan - Meier 5-years survival period is higher than 85%, phase III is 65%; Stage IV 45%, this rate compared to the authors in the world is nearly equivalent. Full 5-year survival for ULAKH with CD 20 (+) for R-therapy - CHOP 84%; CHOP regimen 65% difference was statistically significant with p <0.001. The study of Le Thanh Tu et al, overall lifetime at 6 years of treatment CHOP + Rituximab 84%; CHOP is merely 39% [5]. Duration of disease-free survival after 5 years of patients treated with R-CHOP regimen 72.5%, CHOP regimen 51.5%, the difference was statistically significant with p <0.05. This result of Tu et al was 70.6% and 48.1% [5], respectively.

Conclusions

Through the study of treatment results for 85 patients with non-Hodgkin's malignant lymphoma spreading large cells with CD (+) treated with R-CHOP regimens compared with CHOP, the following conclusions are reached: Average age at diagnosis guessed 46. The highest age at 50 to 59 years of age accounted for 51% of group A and 50% in group B; the age group ≥ 70 accounts for a low rate of 6.7% of group A and 7.5% of group B. Stage IV accounts for the highest rate of 40.0% in both groups, followed by stage III, accounting for 31%. 1% of group A and 32.5% of group B, phase II accounted for 28.9% of group A and 27.5% of group B. The disease met completely accounted for a high rate of 80.0% in group A and 65% in group B. Partial response accounted for 17.8% of group A and 27.5% of group B. Progressive disease met 01 patient in group B. The main toxicity of the regimen on red blood cell formation level I is 64.4% of group A; 57.5% of group B. Leukopenia Grade I 71.1% of group A and 65.6% of group B. The R-CHOP regimen increased the rate of complete response to pure CHOP regimen and this difference was evident when monitoring the overall survival time after 5 years of higher

R-CHOP treatment patients CHOP regimen was 19% and the disease-free survival time after 5 years of patients treated with R-CHOP (72.5%) was higher than that of CHOP (51.5%).

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