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**Research Article**

# Tolerability of Rituximab CHOP(Cyclophosphamide, Hydroxydaunorubicin, Oncovin and Prednisolone) regimen for follicular lymphoma

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## ABSTRACT

**Background And Objective**: Many clinical trials conducted in the western population have shown that the addition of Rituximab to CHOP regimen provided a higher response rate and excellent early survival in follicular lymphoma. This study aimed to assess the tolerability to Rituximab-CHOP regimen for Follicular lymphoma in Indian population.
**Methods**: From January 2015 to January 2016, 32 patients with histopathologically proven denovo follicular lymphoma who were prescribed. Rituximab-CHOP regimen once every 21 days for 6-8 cycles were included in the study. Adverse events causing non compliance to chemotherapy schedule were studied. Causality assessment and grading of severity were done for the above adverse events.
**Results And Discussion**: Age range of the study population was from 37-83 years.78.125% patients were males. Most of the patients belonged to Ann Arbor Stage III/IV. Adverse events causing noncompliance included Infusion related reaction in two patients which was certainly related to Rituximab with a toxicity grade 3 and febrile neutropenia (possibly caused by Doxorubicin with toxicity grade 3 ), leukopenia ( possibly caused by Doxorubicin or Vincristine with a toxicity grade 2 ) and pancytopenia ( possibly caused by Cyclophosphamide or Doxorubicin or Vincristine with a toxicity grade of 3 ) in one patient each.
**Conclusion**: Adverse drug reactions caused by Rituximab and possibly by Doxorubicin, Vincristine or Cyclophosphamide were a reason for non compliance.

**Key Words**: *Adverse event; follicular lymphoma; non compliance; Rituximab; Rituximab-CHOP regimen; tolerability*

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## INTRODUCTION

Lymphomas make up 3–4% of all cancers, making them the seventh-most common form[1]. Non-Hodgkin's lymphomas (NHL) are neoplastic transformations of mature B, T and natural killer (NK) cells. Follicular lymphoma (FL) is the most common indolent lymphoma and the second most common non-Hodgkin lymphoma[2,3]. NHL infiltrates lymphohematopoietic tissues and are among the most sensitive malignancies to radiation and cytotoxic therapy.

Rituximab-CHOP (Cyclophosphamide, Hydroxydaunorubicin, Oncovin and Prednisolone) regimen is a chemotherapy regimen for follicular lymphoma. The rationale behind conducting this study is to obtain reliable data regarding response and tolerability of Rituximab –CHOP regimen for follicular lymphoma in Kerala population.

## AIM

A prospective single arm observational study on the tolerability of patients to Rituximab CHOP regimen for follicular lymphoma given in a teritiary care setting

## OBJECTIVE

To study the tolerability of patients to Rituximab CHOP regimen for follicular lymphoma

## STUDY DESIGN AND SETTING:

A prospective single arm observational study in the Department of Radiotherapy, Medical College, Thiruvananthapuram, with 32 consecutive patients diagnosed by histopathology to have de novo follicular lymphoma and planned to be started on Rituximab -CHOP regimen, from the date of Ethical clearance (09/01/2015), for a period of one year (IEC No: 01/33/2015/MCT)

**MATERIALS AND METHODS:**

i) Selection and description of participants

Study Design- Prospective single arm observational study.
Study Setting- Department of Radiotherapy, Government Medical College, Thiruvananthapuram.
Study Period – January 2015 to January 2016.
Study Population– Patients with histopathologically proven denovo follicular lymphoma who are prescribed R-CHOP regimen.
Sample Size – Thirty two
Sample size calculation: The response rate to Rituximab CHOP regimen among patients with follicular lymphoma is 75% [4].

This finding is used to calculate the sample size of the current study.
Sample size, $n = ( t \alpha/z )^2 pq / d^2$
Response rate , p = 75% Precision , d = 20 % of p Significance level = 5% n = 32
Sampling technique : Consecutive patients attending Radiotherapy OPD, diagnosed to have follicular lymphoma and started on Rituximab CHOP regimen.

**Inclusion criteria :**

- Patients with histopathologically proven denovo follicular lymphoma started on Rituximab CHOP regimen who have not received any other disease specific treatment.
- Patients who give informed consent.
- Age above 18 years.
- Both males and females.

**Exclusion criteria:**

- Pregnancy and breast feeding patients.

ii) Technical information

**Study tools**

1) Chemotherapy Protocol
2) Semi structured questionnaire
3) Revised response criteria for malignant lymphoma
4) Informed consent form – English and Malayalam
5) FLIPI (Follicular Lymphoma International Prognostic Index ) .

**Study procedure**

Rituximab CHOP regimen is given in the Department of Radiotherapy, Government Medical College, Thiruvananthapuram on an outpatient basis once every 21 days for 6 – 8 cycles. Patients satisfying inclusion criteria were enrolled into the study until the required sample size was attained. A total of two visits were done per patient. During the first visit, after obtaining informed consent, semi structured questionnaire and chemotherapy protocol were filled. Adherence to the chemotherapy schedule was enquired by telephonic interview with the patient on the day prior to each cycle. The second visit to the patient was on the day of the last cycle, when compliance was assessed, by comparing initial schedule with the schedule undergone. If an adverse event was found to have caused noncompliance, WHO – UMC Causality assessment system was used. NCI toxicity criteria were then used to grade the severity of those events .Tolerability refers to the degree to which side effects of a drug are tolerated by a patient. Non compliance percentage due to adverse events is a measure of tolerability in this study.

Rituximab-CHOP Regimen (Rituximab – Cyclophosphamide, Hydroxydaunorubicin, Oncovin and Prednisolone) with adjuvant medications : 1) Inj. Ondansetron 8mg IV single dose 2) Inj. Paracetamol 1g IM single dose 30 minutes prior to Rituximab 3) Inj. Pheniramine maleate 25mg single IV bolus 30 minutes prior to Rituximab 4) Inj. Dexamethasone 16mg single IV bolus 30 mins prior to Rituximab 5) T. Prednisolone 20mg 3-0-2 for 5 days. First dose given 30 mins prior to Rituximab 6) Inj. Rituximab 375mg/m2 IV infusion in 500ml 0.9% NaCl 7) Inj. Cyclophosphamide 750mg/m2 IV bolus Methodology 34 8) Inj. Doxorubicin 50mg/m2 IV infusion over 30 minutes 9) Inj. Vincristine 1.4mg/m2 IV over 5 – 10 minutes 10) Inj. Ranitidine 50mg IV single dose 11) . T. Allopurinol 300mg oral od for 1-2 cycles 12) T. Pantoprazole 40mg bd for 10 days 13) T. Ondansetron 8mg tds for 8 days

iii) Statistics : Data is analysed using descriptive statistics (proportions and percentages).

**RESULTS**

The present study was conducted in the department of Radiotherapy, Government Medical College, Trivandrum between January 2015 and January 2016 in thirty two patients with the diagnosis of histopathologically proven de novo follicular lymphoma. They were prescribed Rituximab-CHOP regimen. Patients who were adequately staged and who have not received any other disease specific treatment were included in the study. Adverse events causing non compliance included infusion related reaction and abnormal peripheral blood cell counts.

**STAGE WISE DISTRIBUTION OF STUDY SUBJECTS:**

Follicular lymphoma is staged based on Ann Arbor staging system adapted for Non Hodgkin's lymphoma .Majority of patients belonged to stage III or IV as given in table 1

Table 1: Table showing number of patients belonging to each stage of follicular lymphoma

| stage | Frequency | Percentage |
|---|---|---|
| I | 0 | 0 |
| II | 4 | 12.5 |
| III | 18 | 56.25 |
| IV | 10 | 31.25 |
| total | 32 | 100 |

**DISTRIBUTION OF CD POSITIVITY AMONG STUDY SUBJECTS** :

All patients included in this study were CD 20 positive by immunohistochemistry.

**CATEGORISATION OF STUDY SUBJECTS BASED ON COMPLIANCE TO CHEMOTHERAPY SCHEDULE :**

Patients who followed the chemotherapy schedule dates were categorized as compliant and others were categorized as non compliant. Twenty five patients were compliant while seven patients were non compliant.

**NON COMPLIANCE DUE TO ADVERSE EVENTS** :

Reason for non compliance was adverse event for five patients while two patients were non compliant due to other reasons. Tolerability refers to the degree to which side effects of a drug are tolerated by a patient. Non compliance percentage due to adverse events is a measure of tolerability in this study. 15.625% of patients in this study didn't tolerate this regimen due to adverse events.

Table 2: Table showing Adverse events , their causality assessment and grading

| Patient identification number | CT cycle number | Adverse event | Suspected drugs | WHO causality category | NCI grade |
|---|---|---|---|---|---|
| 1 | 3,4 | Infusion related reaction | Rituximab | Certain | 3 |
| 3 | 3,4 | Infusion related reaction | Rituximab | Certain | 3 |
| 8 | 2 | Febrile neutropenia | Doxorubicin | Possible | 3 |
| 10 | 3 | White blood cell decreased | Doxorubicin, Vincristine | Possible | 2 |
| 31 | 2 | Pancytopenia | Cyclophosphamide, Doxorubicin, Vincristine, | Possible | 3 |

**ADVERSE EVENTS CAUSING NON COMPLIANCE :**

As given in table 2, out of the thirty two patients studied , five were non compliant due to adverse events. Adverse events which led to non compliance to chemotherapy schedule included infusion related reaction in two patients ; febrile neutropenia, decreased white blood cell count and pancytopenia in one patient each. Infusion related reaction occurred during third and fourth cycles for two patients. In both the patients CHOP was given on day 1 and Rituximab was given on day 2 of each cycle .The reaction occurred first during the third infusion of Rituximab and repeated during fourth infusion of Rituximab. So, there is plausible time relation for reaction with Rituximab infusion and re challenge data is satisfactory. Hence infusion related reaction is considered to be certainly due to Rituximab. The adverse event is graded 3 according to NCI toxicity grading criteria CTCAE version 4 as the reaction did not respond promptly to symptomatic

medication and prolonged hospital stay. Febrile neutropenia was possibly caused by Doxorubicin. Leukopenia can be caused by Doxorubicin or Vincristine. Cyclophosphamide, Doxorubicin or Vincristine can cause pancytopenia.90 Patient who developed febrile neutropenia had absolute neutrophil count of 980/mm3 and body temperature > 1010 F, hence grade 3. Patient who developed leucopenia had WBC count of 2100/mm3 , hence grade 2 toxicity. Patient who developed pancytopenia required hospitalization and had limitation of ADL, hence grade 3 toxicity according to NCI toxicity grading criteria CTCAE version 4.

**DISCUSSION**

Rituximab CHOP regimen has the highest efficacy ever described with any chemotherapy in follicular lymphoma[5]. Addition of Rituximab to chemotherapy has made significant improvements in response rate and progression free survival of patients with follicular lymphoma[6-8]. This study was undertaken to study the response of follicular lymphoma to R-CHOP regimen. Secondary objective was to assess the tolerability of patients to this regimen by listing the adverse events leading to non compliance to R-CHOP regimen followed by causality assessment and grading of toxicity. According to FLIPI, patients with age less than 60 years have better prognosis when compared to those with age greater than 60 years. In the present study, 24 patients were less than 60 years and 8 patients were more than 60 years of age. Age range of patients included in this study was from 37 to 83 years which is same as that in a study by M.J. Overman et al[9]. FL has slight female preponderance[10,11]. The present study included 25 males and 7 females. In this study, 87.5% patients had stage III or IV disease compared to a study by M.J. Overman et al which had 80 % patients with stage III or IV disease[9]. All patients in this study were CD 20 positive by immunohistochemistry, as in a study by Myron S. Czuczman et al.[12], In this study, according to FLIPI score, 16% patients were low risk, 31% intermediate risk and 53% high risk. In a study by Samuel A. Jacobs et al, the corresponding figures were 25%, 33% and 42%.[13] In the present study, CR rate after R CHOP was 40.625%. In a study by Samuel A. Jacobs et al, complete response rate was 40%.[13].

**Limitations of the study** - This study was a prospective observational study. For better assessment of efficacy, a randomized controlled trial is preferable. Sample size was small. Larger sample size will yield a better picture of FL in Indian population.

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