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Original Article

Disease Response Rate to Rituximab-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 cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisolone (CHOP) regimen provided a higher response rate and excellent early survival in follicular lymphoma. This study aimed to assess the disease response rate to Rituximab-CHOP regimen for follicular lymphoma in Indian population.

Methods: From January 2015 to January 2016, 32 patients with histopathologically proven *de novo* follicular lymphoma who were prescribed Rituximab-CHOP regimen once every 21 days for 6–8 cycles were included in the study. Disease response rate at 1 month after completion of chemotherapy regimen was studied.

Results and Discussion: Age range of the study population was from 37 to 83 years. About 78.125% patients were male. Most of the patients belonged to Ann Arbor Stage III/IV. About 90.625% patients showed positive response to treatment at the end of 1 month after completion of chemotherapy schedule.

Conclusion: Response rate to treatment with Rituximab-CHOP regimen at the end of 1 month after completion of chemotherapy schedule was 90.625.

Key words: Disease response rate, Follicular lymphoma, Rituximab, Rituximab-CHOP regimen

INTRODUCTION

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

Rituximab-cyclophosphamide, Hydroxydaunorubicin, Oncovin, and Prednisolone (CHOP) regimen is a chemotherapy regimen for follicular lymphoma. This study assesses the disease response rate to this regimen for follicular lymphoma in Indian population.

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Aim

This study was a prospective single-arm observational study on disease response rate to Rituximab-CHOP regimen for follicular lymphoma given in a tertiary care setting.

Objective

The objective of this study was to study the disease response rate 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-

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CHOP regimen, from the date of ethical clearance (January 09, 2015), for a period of 1 year (IEC No: 01/33/2015/MCT).

MATERIALS AND METHODS

Selection and Description of Participants

Study Design

This study was prospective single-arm observational study.

Study Setting

This study was Department of Radiotherapy, Government Medical College, Thiruvananthapuram.

Study Period

This study was January 2015 to January 2016.

Study Population

This study was patients with histopathologically proven *de novo* follicular lymphoma who are prescribed R-CHOP regimen.

Sample Size

The sample size was 32.

Sample size calculation

The response rate to Rituximab-CHOP regimen among patients with follicular lymphoma is 75%.[3]

This finding is used to calculate the sample size of the present 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

The following criteria were included in the study:

- Patients with histopathologically proven *de novo* 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

The following criteria were excluded from the study:

- Pregnancy and breastfeeding patients.

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. Follicular lymphoma international prognostic index (FLIPI).

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. 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 before each cycle. Department of radiotherapy follows revised response criteria for malignant lymphoma to assess the disease response rate. Disease response rate is the percentage of patients who attain positive response to treatment at a specific time. During the visit at 1 month after completion of chemotherapy regimen, these criteria were used to categorize response of each patient and disease response rate is calculated.

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

Statistics

Data are analyzed 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 32 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. Assessment of disease response was done and results analyzed. Majority of patients showed positive response to treatment.

Stage-Wise Distribution of Study Subjects

As given in Table 1, 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.

Distribution of CD Positivity among Study Subjects

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

Categorization of Study Subjects Based on FLIPI Score

FLIPI is a scoring system based on which patients can be categorized into high, intermediate and low risk groups and 5 year and 10 year overall survival percentages have been predicted. As given in Table 2, five patients belonged to low risk, ten patients to intermediate risk, and 17 patients to high risk group.

Disease Response

Disease response was categorized based on Revised Response Criteria for malignant lymphoma comparing physical examination and imaging studies done before start of chemotherapy and 1 month after completion of chemotherapy. As per these criteria, there can be complete remission/partial remission/stable disease/relapsed disease (after complete remission) or progressive disease (after partial remission/stable disease). The present study assesses only the initial response to treatment which is done 1 month after completion of chemotherapy regimen. Hence, patients are categorized to have attained complete remission/partial remission/stable disease only. They may remain in remission or stable disease or they may develop relapse (after complete remission) or progression of disease (after partial remission or stable disease). At 1 month after completion of chemotherapy, 13 patients attained complete remission, 16 patients attained partial remission, and three patients had stable disease.

Table 1: Number of patients in 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

Positive and Negative Response to Treatment

In a study by Papaioannou *et al.*, complete remission and partial remission are together categorized as positive response to treatment and the rest as negative response to treatment.[4] Disease response rate is the percentage of patients who attain positive response to treatment at a specific time. In this study, 1 month after completion of chemotherapy, 29 patients showed positive response to treatment and three patients showed negative response to treatment. As per this study, disease response rate to RCHOP regimen for follicular lymphoma is 90.625% at 1 month after completion of chemotherapy. All patients whose response was assessed using Positron Emission Tomography (PET) scan showed positive response to therapy.

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 <60 years have better prognosis when compared to those with age >60 years. In the present study, 24 patients were <60 years and eight 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 Overman *et al.*[9] FL has slight female preponderance.[10,11] The present study included 25 males and seven females. In this study, 87.5% patients had

Table 2: Risk categorization of patients

Risk category	Predicted 5year OS (%)	Predicted 10 year OS (%)	Frequency	Percentage
Low	91	71	5	15.625
Intermediate	78	51	10	31.25
High	52	59	17	53.125
Total				100

stage III or IV disease compared to a study by 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 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 Jacobs *et al*., the corresponding figures were 25%, 33% and 42%.97. In the present study, CR rate after R CHOP was 40.625%. In a study by 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. Response was assessed based on CT scan in majority of cases. We cannot determine if residual enlarged nodes by size criteria contain viable lymphoma. PET is a better alternative as a functional imaging tool for staging and response assessment of lymphomas.

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