
Chemoimmunotherapy resistant follicular lymphoma – A single institutional study

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To cite this article:

Sampath Kumar-Kandala Jeevan, Roshni Paul-Tara, Shantiveer Uppin, Megha Uppin, Kavitha Bali, Sundaram-Challa, Raghunadha Rao. Chemoimmunotherapy Resistant Follicular Lymphoma – A Single Institutional Study. *Cancer Research Journal*.

Vol. 2, No. 5, 2014, pp. 93-97. doi: 10.11648/j.crj.20140205.13

Abstract: Follicular lymphoma (FL) is the most common indolent form of non Hodgkin lymphoma and characterized by initial response to treatment with inevitable relapse. Rituximab, is an anti CD20 monoclonal antibody, plays an important role in combination chemoimmunotherapy in treatment of symptomatic follicular lymphoma. Though rituximab is helpful in reducing the tumor burden in patients of follicular lymphoma, a significant proportion of patients were found to have resistance to rituximab and eventually progressed to high grade lymphoma. In this study we evaluated chemoimmunotherapy (CIR) resistant patients to know the incidence, predictive factors associated with CIR resistance and prognosis. This is a retrospective study, included 49 patients of follicular lymphoma, of these 12 (24.5%) demonstrated CIR resistance. On univariate analysis, high LDH values, advanced stage and high FLIPI score may predict the resistance of CIR therapy in initial stage of therapy. Overall, 7 patients (58.3%) progressed to high grade lymphoma (biopsy proven) and 2 (16.6%) died of disease progression in CIR resistant patients. Progressive free survival significantly reduced in CIR resistant patients (26 months) than CIR responders.

Keywords: Chemoimmunotherapy Resistance, Follicular Lymphoma, FLIPI Score, Lactate Dehydrogenase, Advance Stage, Progression

1. Introduction

Follicular lymphoma (FL) is an indolent non hodgkin lymphoma characterized by an initial response to treatment but inevitable relapse. In the last decade, immunotherapy with anti CD20 monoclonal antibody, Rituximab, modified the therapeutic approach of B-cell non-hodgkin lymphoma(1). Conventional chemotherapy does not alone cure the follicular lymphoma but combining the chemotherapy with monoclonal antibody therapy has better results to the same chemotherapy alone, so concomitant chemoimmunotherapy has become first line treatment for follicular lymphoma(2). However, a subset of patients will show disease progression during initial Chemoimmunotherapy or maintenance phase of rituximab based therapy. The true incidence of chemoimmunotherapy resistant to rituximab is unknown, estimates range from

14% in patients receiving rituximab as a part of primary therapy to 28% for those receiving chemoimmunotherapy and maintenance rituximab as second line treatment (3,4,5). Disease progression during treatment may result from resistance to chemotherapy, rituximab or to combined therapy. Mechanisms of resistance to rituximab have not been fully elucidated but may include the over-expression of complement inhibitory molecules CD55 and CD59 [6-7], under-expression of CD20 (8-10) and decreased affinity of rituximab to the Fc receptor resulting in reduced antibody-dependent cell-mediated cytotoxicity (11, 12).

Transformation of follicular lymphoma to a more aggressive histology occurs at an annual rate of 3% from date of diagnosis, with a 10-year risk of approximately 30% in the pre-rituximab era (13). Transformation confers a poor prognosis with a median post-transformation survival of 1 to 2 years (13) and 5- year survival of 25% (13-16). Main aim

of our study is to determine the incidence, predictive factors association with histological transformation and outcome of CIR resistance in rituximab therapy.

2. Material and Methods

Patients were retrospectively identified using clinical database from single center. Patients with a diagnosed of FL grade 1, 2 and 3a according to the WHO classification were included in this study. Exclusion criteria included composite or discordance lymphoma and FL grade 3b. Baseline characteristics were recorded and included histology, advanced stage disease (stage III or IV) FLIPI risk score.

2.1. Chemoimmunotherapy Resistance Definition

CIR resistance was defined as either resistance to initial chemoimmunotherapy or to maintenance rituximab within 6 months of treatment completion.

2.2. Transformation Definition

Determination of transformation was based on a biopsy demonstrating FL grade 3b, diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL) or B-cell lymphoma unclassifiable with features intermediate between DLBCL and BL as per WHO 2008 classification (17).

2.3. Outcome Definition

PFS was measured from initiation of rituximab-based chemoimmunotherapy to radiological or clinical progression as determined by the treating clinician/oncologist. OS was measured from the initiation of rituximab chemoimmunotherapy until last follow-up or death. PFS was calculated using the Kaplan-Meier method. Chi-square test was used for univariate calculation of clinically relevant predictors for early progression. All statistical calculations were made using Graph Pad Prism, version 5.00 software.

3. Results

This retrospective study comprises 68 cases of follicular lymphomas included over a period of four years (2007-2011) in our institute. Nineteen patients were excluded from this study for the following reasons: fifteen patients were lost to follow-up and four patients were treated as diffuse large B-cell lymphoma. Therefore, 49 patients were identified as receiving rituximab based chemoimmunotherapy. Of these, twelve patients (24.5%) were resistant to immunochemotherapy. Of these CIR resistance patients, seven were progressed during initial chemoimmunotherapy, three during maintenance therapy and two within 6 months after maintenance completion. From initiation of rituximab containing chemoimmunotherapy, median follow-up was 36 months (range from 6 months to 60months). Baseline characteristics of CI responder and CIR resistant group described in Table-1.

3.1. Clinical and Characteristics of Chemoimmunotherapy Resistance Patients

Of 49 patients, twelve (24.5%) patients developed resistant to combination of rituximab and chemotherapy. There was a male predominance with M: F ratio of 1.4: 1. All CIR resistant patients (24.5%) were biopsied at the time of disease progression and all these patients were demonstrating evidence of disease progression. Of 12 patients, 5 were confirmed to have diffuse large B-cell lymphoma and 2 were B-cell lymphoma unclassifiable with features of DLBCL and Burkitt lymphoma. Outcome and follow-up of CIR resistant with disease progression are shown in Table-2. In univariate analysis, rituximab based chemoimmunotherapy resistance group had statistically significance in association with high lactate dehydrogenase enzyme value ($p=0.0005$, figure-1A), advanced stage ($p<0.0001$, figure-1B) and high FLIPI score >3 ($p=0.0005$, figure-1C). Factors which were not statistically significant include, gender ($p=1.0$), histological grade ($p=0.4589$). Of 12 patients who resistance to therapy, eight achieved partial remission with R-CHOP treatment and remaining three were not responded to the treatment. During follow-up, 2 deaths occurred in CIR resistant group.

Table 1. Baseline characteristics of CIR responder and CIR resistant group

Characteristics	CIR responder (n=37)	CIR resistance (n=12)
Age	56	58.3
Gender (female)	43.2%	41.6%
Histological grade		
Grade 1	22 (59.4%)	6 (50%)
Grade 2	13 (35.1%)	4 (33.3%)
Grade 3a	2 (5.4%)	2 (16.6%)
Bone marrow involvement	20 (54%)	9 (75%)
FLIP score		
Low (0,1,2)	24 (64.8)	2 (16.6%)
Intermediate (3)	10 (27%)	3 (25%)
High (4 or 5)	3 (8.1%)	7 (58.8%)
Stage 3 or 4	26 (70.2%)	12 (100%)
High grade lymphoma transformation	No	7 (58.3%)

Abbreviations: CIR responder - chemoimmunotherapy or maintenance rituximab responder, CIR resistance- chemoimmunotherapy or maintenance rituximab resistance.

4. Discussion

Rituximab is most widely used anti-CD20 monoclonal antibody, and has dramatically improved outcomes for patients with follicular lymphoma (1). This monoclonal antibody (rituximab), when combined with chemotherapy it will improve the both response rate and the progression free survival (rituximab for the treatment) in relapse or resistant FL. Although rituximab is useful in untreated and relapse follicular lymphoma, however few patients develop resistance to rituximab along with histological transformation (13,18) into high grade lymphoma, which remains clinical challenge for most of the clinicians. In this

study were trying to discuss the factors which are associated with resistance and transformation of follicular lymphoma and also prognosis of chemoimmunotherapy resistant patients. Our primary aim was not to distinguish between rituximab with combination therapies and rituximab therapy alone.

This is a retrospective study, comprising of 49 patients of symptomatic follicular lymphoma. Of these, 24.5% of patients were showing resistant to rituximab combination therapy. Incidence of our study is slight higher than recently published study (2014). There were studies showed that measures of tumor burden includes, FLIPI score and stage of the disease correlate with disease progression (13,14, 15). High FLIPI score, high serum LDH and advanced stage were predictive of CIR resistance in univariate analysis in

this study, which is similar to Mozessohn et al study and other studies (18). But gender and histological grade were not reached the statistical significance in univariate analysis and this is probably due to small study group.

Not surprisingly, patients with chemoimmunotherapy resistance were found to have with transformation and reduced progressive free and overall survival. Al-Tourah et al (13) reported that rituximab with combination chemotherapy for follicular lymphoma the five year transformation rate was less than 10%. Mozessohn et al (18) reported the rate of transformation was 36.3% in those receiving chemoimmunotherapy during or after 6 months of maintenance of rituximab. But in our study, we found much higher rate of transformation of 58.3% than previously described studies (13, 18).

Table 2. Characteristic features and prognosis of CIR resistant patients

Patient	Age at diagnosis	Biopsy proven transformation	Timing of resistance	Pathology at transformation	BM involvement	Treatment after post transformation	Response to treatment post transformation	Death
1	58	Yes	During initial therapy	N/A	Yes	R-CHOP X4	PD	Yes
2	61	Yes	After MR	DLBCL	Yes	R-CHOP X6	PR	No
3	56	Yes	During MR	N/A	No	R-CHOP X6	PR	No
4	62	Yes	During Initial therapy	Large B-cell lymphoma	Yes	R-CHOP X6	PR	No
5	60	Yes	During initial therapy	DLBCL	Yes	R-CHOP X6	PR	No
6	45	Yes	During initial therapy	DLBCL	Yes	R-CHOP X6	PR	No
7	70	Yes	During MR	Large B-cell lymphoma	Yes	R-CHOP X6	PR	No
8	70	Yes	During MR	N/A	Yes	R-CHOP X6	PR	No
9	73	Yes	During initial therapy	DLBCL	Yes	R-CHOP X2	PD	Yes
10	58	Yes	During initial therapy	DLBCL	Yes	R-CHOP X6	PR	No
11	38	Yes	During initial therapy	N/A	No	R-CHOP X6	PD	No
12	55	Yes	After MR	N/A	No	R-CHOP X6	PD	No

Abbreviations: DLBCL – Diffuse large B-cell lymphoma, MR – maintenance rituximab, PD- progressive disease, PR-partial remission, R-CHOP-rituximab, cyclophosphamide, vincristine, doxorubicin, prednisone

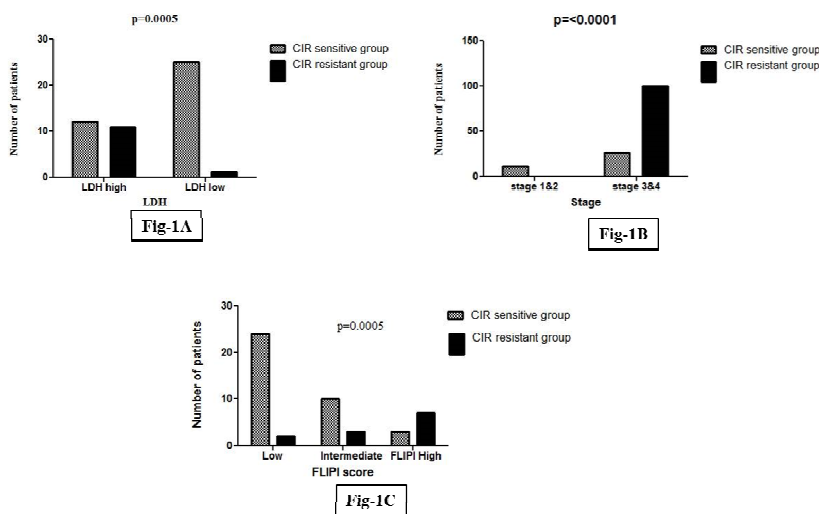


Fig 1. Comparison of LDH levels (Fig-1A), Stage (Fig-1B) and FLIPI Score(Fig-1C) of the disease among CIR responder and resistant group

Studies showed that R-CHOP regimen with long follow-up found to have improved progressive free survival and decrease the tumor burden relapsed or resistant follicular lymphoma. Marinus et al (5), they randomly assigned 465 patients to induction with either six cycles of CHOP or R-CHOP and those in complete remission or partial remission after induction were randomly assigned to maintenance treatment with rituximab. In their study, they showed that significantly increased progressive free survival in R-CHOP group (3.7 years) than observation group (1.8 years) and also confirmed that superior PFS with rituximab in resistant or relapse FL. However studies showed that prolonged maintenance therapy with rituximab resulting in relapse or resistance in follicular lymphoma and the possible mechanisms for resistance to rituximab is due to mutations in CD20 gene (20), over-expression of complement inhibitory molecules CD55 and CD59 [6-7], under-expression of CD20 (8-10). Marinus et al reported that progression and relapse rate of 35% to 40% occurring during or within 6 months of after maintenance of rituximab treatment.

In our study, chemoimmunotherapy resistant patients had taken R-CHOP regimen as a first line of treatment. Of these patients, eight patients (66.6%) showed partial response to treatment and remaining patients (33.3%) were not responded to treatment and two were died because of disease progression. Compared to Chemoimmunotherapy responder group, in CIR resistant group had significantly reduced progressive free survival (26 months vs. not reached, $p < 0.0001$, figure-4), which is higher than Mozessohn et al study (18) and overall survival did not reach statistical significance ($p = 0.0561$), probably due to small study population group.

5. Conclusion

Despite of rituximab based chemoimmunotherapy, a significant proportion of patients are developing resistant to treatment and disease progression. In this study, high LDH values, advanced stage and high FLIPI score may predict the risk of resistance to chemoimmunotherapy at the time initial treatment. Progressive free survival was significantly reduced in CIR resistant patients than CI respond patients. So this is time to discover newer regimen to overcome the resistance to rituximab based therapy and also to decrease the rate of disease progression of follicular lymphoma.

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