# Safety Profile of Rituximab In 100 Adults Patients With B-Lymphoproliferative Disorders

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**ABSTRACT :**

**BACKGROUND:**

Non-Hodgkin lymphoma (NHL) is the most common hematologic cancer in adults. Rituximab is a chimeric anti-CD20 monoclonal antibody that transformed the outcome of the B-lymphoproliferative disorders . Treatment with rituximab is relatively safe but occasionally serious.

**OBJECTIVE:**

To evaluate the safety of Rituximab in the treatment of Iraqi adult patients with B-lymphoproliferative disorders.

**PATIENTS AND METHODS**:

A total of 100 patients with low grade, high grade B-cell non-Hodgkin lymphoma and chronic lymphocytic leukemia (CLL) who were admitted to the Haematology unit of Baghdad Teaching Hospital to receive their scheduled Rituximab containing protocol were included in this cohort prospective study between April 2011 to march 2012 .The patients were divided into two groups according to the presence or absence of infusional side effects of rituximab. Infusional side effects of rituximab were recorded with each dose and correlate them with certain patients' parameters including age, gender and serum LDH .

**RESULTS:**

Fever (36%), Rigor (28%) and nausea and vomiting (23%) were the most prevalent infusional side effects of rituximab in both NHL and CLL, with most of these infusional side effects occur in the first infusion**.** One treatment related mortality occurred. Infusional side effects of rituximab were more prevalent in CLL than other patients with NHL (P=0.0005) and in those with normal serum LDH(P=0.046)

**CONCLUSION:**

Rituximb-induced infusional side effects in this study are more common in the first infusion, and patients with CLL . Most of infusional side effects are mild of grade one or two although one fatal side effect had occurred.

**KEY WORDS:** rituximab , lymphoproliferative disorders.

## INTRODUCTION:

Non-Hodgkin lymphoma (NHL) is a non-specific term that includes several lymphoproliferative malignant diseases with different clinical and histological appearances[(1)], it is the most common hematologic cancer in adults and is a heterogeneous group of cancers arising from B or T lymphocytes, also rarely from NK cells [(2,3)].On 1997, rituximab became the first monoclonal antibody approved by the Food and Drug Administration (FDA) for the treatment of a human cancer — relapsed or refractory, low-grade (indolent) or follicular, CD20+ non-Hodgkin's lymphoma[(2)].

Rituximab is a chimeric monoclonal antibody produced by recombinant technology. It binds specifically to CD20, an antigen expressed by most human B lymphocytes. Rituximab was created by fusing the light- and heavy-chain variable domains of 2B8, a murine monoclonal anti-CD20 antibody and human κ light-chain and γ1 heavy-chain constant regions[(4)].

The efficacy of rituximab in combination with chemotherapeutic agents has been evaluated in several clinical trials in patients with B-cell NHL, and clinical response rates are encouraging[(5)].

Approximately 84% of patients experienced an adverse event during therapy or within the first 30 days following treatment. However, adverse events were typically mild to moderate in severity (>95% were grade 1 or 2 according to NCI Common Toxicity Criteria), of brief

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duration (e.g. nausea for 1 hour, fever for 3 hours), and observed during the first infusion [5].

The aim of this study is to evaluate the safety and infusional side effects of anti-CD20 monoclonal antibody (Rituximab) and to assess the risk of reactivation of hepatitis B virus infection after treatment with this monoclonal antibody in B-lymphoproliferative disorders.

## PATIENTS AND METHODS:

From April 2011 to March 2012, 100 patients with B-cell non-Hodgkin lymphoma(B-NHL) and chronic lymphocytic leukemia (CLL) were included in this cohort prospective study.

The patients were recruited from haematological ward at Baghdad Teaching Hospital/Medical City. The diagnosis of B-cell NHL was based on the histopathological examination of biopsy from involved lymph node or biopsy from affected organ then stained with CD20 by immunohistochemistry to confirm B-cell origin.

The treatment protocol containing Rituximab was decided according to the local management guidelines of the hematology unit. The written consent was obtained for all patients before initiation of treatment.

The data sheet included baseline information (name, age, gender, mobile number –for follow up).

All patients were subjected to following investigations:

- Complete blood count,blood urea ,serum creatinine, serum bilirubin, Alanine aminotransferase ، Aspartate aminotransferase , Serum alkaline phosphatase and Lactate dehydrogenase .
- Bone marrow aspiration and biopsy.
- ECG and echocardiography of the heart before starting chemotherapy to assess cardiac status.
- Ultrasonography of the abdomen, CT scan of the abdomen and chest.
- Virology study ( HCV Ab , HBsAg , HBsAb , HBeAg , HBeAb , HBcAb ) were before starting therapy and after completing the treatment .The results are expressed as positive &negative.

Before each dose of rituximab (MabThera ,Roche, Germany ) , the patients received premedication with intravenous chlorpheniramine ,corticosteroid (either hydrocortisone 100mg or dexamethasone 8mg) and oral paracetamol 1000 mg ,the first infusion was given slowly over 6 hours then the subsequent doses given over 2 hours with monitoring of vital signs before ,1 hour through and after the finishing the infusion with hydrocortisone 100mg injection, chlorpheniramine injection, adrenaline ampoule, oxygen available to manage any anaphylactic reaction that may occur.

Infusional side effects of rituximab were recorded for each dose according to Common Terminology Criteria for Adverse Events v3.0 [7].

The patients were studied regarding their age, gender, diagnosis, stage, outcome and we divided them into two groups according to the diagnosis (CLL vs. NHL).

We divided the patients into two groups according to the appearance of infusional side effects of rituximab (patients with or without side effects).

For all patients we recorded the appearance of side effects of rituximab with each dose and correlate them with certain parameters like age, gender, serum LDH and diagnosis.

**Statistical analysis:**

SPSS (statistical package for social sciences), version 18\ IBM.US.\2007, software for windows was used for entering and analysis of data. Descriptive statistics of different variables were performed as (mean ± standard deviation(SD)), ranges, or frequencies and percentages. *Yates* corrected Chi square ($X^2$) or Fisher exact test were used for comparison among categorical variables for frequencies and percentages. Students' independent two samples *t* test was used for comparison of means in between groups of patients (NHL group and CLL group) or within group for comparison of mean age and mean WBC count in patients with side effects to those without.

In all statistical analysis, level of significance ≤ 0.05 was assumed to indicate statistically significant difference.

## RESULTS:

There were 100 adult patients in this study , 64 (64%) were females and 36 (36%) were males; on the other hand they were 24 (24%) CLL patients and 76(76%) NHL patients, the mean age of the patients was (52.2 ± 15.6) years, (table 1).

**Table 1: Patients characteristics.**

| Characteristic | | Number | % |
|---|---|---|---|
| Age (in years) | | | |
| | Mean ± SD* | 52.2 ± 15.6 | |
| | Range | 20 – 85 | |
| Gender | | | |
| | Female | 64 | 64% |
| | Male | 36 | 36% |
| Diagnosis | | | |
| | B-NHL | 76 | 76% |
| | CLL | 24 | 24% |

*SD standard deviation.

There were 76 patients with NHL with mean age (50.1 ±16) years, range from 20-85 years, 47(61.8%) of them were females whereas 29(38.2%) were males. Eleven (14.5%) patients were relapsed cases, and 65 (85.5%) patients were treatment naive. Bulky disease was seen in 9(11.8%) patients, normal LDH was recorded in 52(68.4%) of patients and elevated LDH was recorded in 24(31.6%) of patients, regarding the grade, indolent type was seen in 29(38.2%) cases while aggressive pathology was seen in 47(61.8%) cases ( table 2).

**Table 2: NHL and CLL Patients Characteristics .**

| Characteristic | NHL Number(%) | CLL Number(%) |
|---|---|---|
| AGE (in years) | | |
| Mean ± SD | 50.1 ± 16 | 58.8 ± 12 |
| Range | 20 – 85 | 37– 77 |
| Gender | | |
| Female | 47 (61.8%) | 17 (70.8%) |
| Male | 29 (38.2%) | 7 (29.2%) |
| Status | | |
| Relapse | 11 (14.5%) | ----- |
| Treatment naive | 65 (85.5%) | 24 (100%) |
| Early/Intermediate (((stage(intermediate for CLL) | 15 (19.7%) | 3 (12.5%) |
| Advanced stage | 50 (65.8%) | 21 (87.5%) |
| Bulky disease | 9 (11.8%) | ------ |
| S.LDH | | |
| Normal | 52 (68.4%) | 20 (83.3%) |
| Increased | 24 (31.6%) | 4 (16.7%) |
| Pathology | | |
| Indolent | 29 (38.2%) | ------ |

| | | |
|---|---|---|
| Aggressive | 47 (61.8%) | ------ |
| Treatment Regimen<br>R-FC*<br>R-CHOP**<br>R-others | <br>23(30.3%)<br>43 (56.6%)<br>10(13.1%) | <br>20 (83.3%)<br>------<br>4 (16.7%) |

*R-FC=Rituximab+Fludarabine+Cyclophosphamide.
**R-CHOP=Rituximab+Cyclophosphamide+Doxorubicine+Vincristine+Prednisolone.

Table 2 also describes the characteristics of CLL patients, the age range was 37-77 years, the mean ±SD was 58.8±12, 17(70.8%) patients were males and 7(29.2%) patients were females.Intermediate stage was found in 3 (12.5%) patients, while advance stage was noticed in 21 (87.5%) patients. Normal LDH was found in 20(83.3%) patients, and increased LDH was found in 4(16.7%).

Table 2 describes Rituximab containing schedules used for treatment of NHL and CLL patients, regarding NHL, 23(30.3%) patients were treated with R-FC, while R-CHOP was used in 43(56.6%) patients. Regarding CLL, 20 (83.3%) patients received R-FC, and the remaining 4 (16.7%) received other protocols like R-ICE and R-DAHAP.

Table 3 describes the infusion related side effects of rituximab, 36(36%) of all 100 patients had fever in the first infusion and 15(15%) patients in the subsequent infusions, rigor was recorded in 28(28%)patients in the first infusion and 3(3%) patients in the subsequent infusions, 8(8%) patient had sweating in the first infusion only,4(4%) patient had pruritus in the first infusion only, headache, dizziness were occurred in 4(4%)and 1(1%) respectively in the first infusion only, palpitation was noticed in 5(5%)patients in the first infusion and 2(2%) patients in the subsequent infusions, dyspnea was found in 12(12%)patients in the first infusion and 3(3%) patients in the subsequent infusions, 23 patients had nausea and vomiting in the first infusion and 5(5%) patients in the subsequent infusions, diarrhoea was seen in 3(3%)patients in the first infusion only, rash was seen in3(3%)patients in the first infusion only, death was encountered in 1(1%) patient. One hour after the start of the infusion the patient started to have fever, rigor, generalized bone pain, sever shortness of breath, with bronchopasm, hypotension, followed by cardiac arrest after transfer to the intensive care unit.

HBsAg seroconversion was recorded in 1(1%) patient without clinically evidenced jaundice or elevation in liver enzymes.

**Table 3:Frequency of Rituximab related side effects.**

| Side effect | First infusion | | Second Infusion and subsequent infusions | |
|---|---|---|---|---|
| | N | Percent | N | Percent |
| Fever | 36 | 36% | 15 | 15% |
| Rigor | 28 | 28% | 3 | 3% |
| Sweating | 8 | 8% | - | - |
| Pruritus | 4 | 4% | - | - |
| Headache | 4 | 4% | - | - |
| Dizziness | 1 | 1% | - | - |
| Palpitation | 5 | 5% | 2 | 2% |
| Dyspnea | 12 | 12% | 3 | 3% |
| Nausea and vomiting | 23 | 23% | 5 | 5% |
| Diarrhoea | 3 | 3% | - | - |
| Rash | 3 | 3% | - | - |

| | | | | |
|---|---|---|---|---|
| Death | 1 | 1% | - | - |
| HBsAg seroconversion | 1 | 1% | | |

Table 4 compares between two groups of patients , those with Rituximab infusion related side effects (36 patients) and those without Rituximab infusion related side effects (64 patients) regarding certain parameters.

It was found that age is not significantly associated with side effects (p=0.65), regarding gender, females had more side effects compared to males although not statistically significant (p=0.25), with regard to the diagnosis, side effects were more prevalent among CLL patients rather than NHL patients (p=0.0005), regarding serum LDH those with normal serum LDH recorded more side effects than those with high serum LDH but the statistical significance was borderline (p=0.046).

**Table 4: Relation Between Rituximab Side Effects and Some Variables.**

| Variable | | Patients with side effect | Patients without side effects | Total | P.value |
|---|---|---|---|---|---|
| Number of patients | | 36 | 64 | 100 | - |
| Age(years) mean ±SD SD | | 51.2 ± 14.2 | 52.8 ± 16.2 | 52.2 ± 15.6 | 0.65 |
| Gender | Male | 21 (32.8%) | 43 (67.2%) | 64 (100%) | 0.25 |
| | Female | 15 (41.7%) | 21 (58.3%) | 36 (100%) | |
| Diagnosis | CLL | 16 (66.7%) | 8 (33.3%) | 24 (100%) | 0.0005* |
| | NHL | 20 (26.3%) | 56 (73.3%) | 76 (100%) | |
| LDH | Abnormal | 6 (21.4%) | 22 (78.6%) | 28 (100%) | 0.046* |
| | Normal | 30 (41.7%) | 42 (58.3%) | 72 (100%) | |

*Statistically significant.

Table 5 compares between two groups those with CLL +indolent NHL(53 patients) and those with aggressive NHL(47 patients), it was found that patients with CLL + indolent NHL had more side effects than those with aggressive NHL (P. Value=0.04 ).

**Table 5: Relation between Rituximab side effects and CLL and indolent NHL patients compared with aggressive NHL.**

| Diagnosis | With Side Effects | Without Side Effects | Total |
|---|---|---|---|
| CLL + Indolent | 24(45.3%) | 29(54.7%) | 53(100.0%) |
| Aggressive | 12(25.5%) | 35 (74.5%) | 47(100.0%) |
| Total | 36(36%) | 64(64%) | 100(100%) |
| Odds ratio = 2.4 | | P.value = 0.04* | |

*Statistically significant.

## DISCUSSION:

In this study of 100 Iraqi patients with B-cell lymphoproliferative disorders who received rituximab based treatment were evaluated. We focused on infusional side effects of rituximab.

In general, rituximab therapy was well tolerated and most infusional side effects were transient and of grade 1 or 2.

Fever, Rigor and nausea and vomiting were the most prevalent infusional side effects in both

NHL and CLL, with most of these infusional side effects occur in the first infusion, these findings were similar to a study done by John D. Hainsworth et al(2001) at the Sarah Cannon Cancer Center Virginia in which 41 patients with low grade NHL were studied for response to rituximab and adverse effects of it [8]. The mechanism by which rituximab elicits infusion reactions remains unclear, although the symptoms associated with the reactions are thought to be related to the release of inflammatory cytokines[9].The most common adverse reactions of rituximab (incidence ≥ 25%) observed in patients with NHL include infusion reactions, the majority of which are mild to moderate (grades 1 and 2) in nature. The incidence of any-grade infusion reactions was highest during the first infusion (77%) and decreased with each subsequent infusion. These infusion reactions generally have resolved with slowing or interruption of the infusion and with supportive care[10]. Diagnosis of CLL was significantly associated with infusional side effects (P=0.0005 ), this finding is similar to study done by Dieter Huhn [11] and study done by Susan O'Brien [12].Huhn etal reported one mortality in 29 patients with B-CLL treated with Rituximab, other side effects included flulike symptoms (52% of the patients), fever (31%), rigors and/or chills (34%), tachycardia (17%), hypotension (10%), vomiting (10%), and headache (7%). Infections of all CTC grades occurred in 7 (24%) of 29 patients[12].

Earlier trials of monoclonal antibodies consistently showed that such reactions occurred predictably in the setting of circulating cells that expressed the antigen being targeted by the monoclonal antibody, but were less in other settings [12], and this may explain that more infusional side effects were found in CLL group in this study.

There is no significant association between age and the infusional side effect.Older patients had more side effects in CLL group in a study done by Dieter Huhn [11]and Robert O. Dillman study in *California, USA*[13].This difference could be explained by the relatively smaller number of elderly patients in this study.

Regarding serum LDH, infusional side effects were more in patients with normal serum LDH level which gives the impression that the tumor bulk reflected by serum LDH level is not much related to infusional side effects.

We correlated between those with CLL+indolent NHL as a group and aggressive NHL as a group in association with rituximab infusional side effects and we found that there is significant association with the CLL+ Indolent NHL group (p=0.04), although this may reflect the addition of CLL group which had highly significant association with rituximab infusional side effects (P=0.0005) to the indolent group of NHL.

One treatment-related death occurred during this study in a 40-year-old female patient with stage IV indolent NHL and without comorbidities, the patient developed fever, rigor, sever shortness of breath and progressive hypotension, clinically she was labeled as a case of severe cytokine release syndrome, infusion of rituximab had been stopped immediately, intravenous hydrocortisone, chlorpheniramine and isotonic saline started and the patient was transferred to the intensive care unit for further management but unfotunately she died few hours later. Administration of rituximab can result in serious—including fatal—infusion reactions. Deaths within 24 hours of rituximab infusion have occurred, and approximately 80% of fatal infusion reactions occurred in association with the first infusion. This highlights the importance of careful monitoring of patients during infusions, and administration should be discontinued and supportive treatment provided for grade 3 or 4 infusion reactions[10].

Reactivation of hepatitis B, though it is not an infusional side effect was encountered in one patient with HBsAg negative and HBcAb positive.

There is much controversy regarding the incidence of HBV reactivation, two studies one done by Winnie Yeo et al [14] and other done by Kosei Matsue et al [6], both studies showed that Combined use of rituximab and intensive chemotherapy is associated with the increased incidence of HBV reactivation in HBsAg-negative but anti-HBc–positive patients with B-cell lymphoma, especially in endemic areas.

## CONCLUSION :

Rituximb-induced infusional side effects in this study wer more common in the first infusion, and in patients with CLL . Most of infusional side effects were mild and of grade one or two although one fatality occurred ,careful monitoring of the patients during infusion is mandatory.

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