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Rituximab in non-Hodgkin Lymphoma (NHL)

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Abstract

Purpose: To study epidemiology of NHL in Tripoli Medical Center (TMC), to assess response rate to rituximab in CD20 positive NHL patients and compare our results with international results.

Methods :

Retrospective non-randomized study includes all patients registered as non Hodgkin Lymphoma in oncology clinic in TMC. 88 patients were registered in the period between Jan 2011 and Dec 2013. 60 patients with CD20 positive B cell Non Hodgkin Lymphoma.

Results:

Median age was 56.5 years, SD±16.14. 62/88 (70%) were high grade NHL. 19/88 (21.3%) were low grade NHL. 5/88(5.7%) were T cell lymphomas. 70/88 (79.5%) were CD20 positive B cell type. 60/70 (86%) patients with CD20 positive B cell lymphomas received Rituximab either with CHOP or CVP. 43.3% were male and 56.7% were female. 23/60 (38.3%) have extra nodal lymphoma. Stomach is being the most common extra nodal organ involved in (56.2%). 37/60(61.7%) were nodal lymphoma. 48/60 (80%) were aggressive large B cell lymphomas, 12/60(20%)were low grade NHL. 7/60 (11.7%) of patients have bone marrow infiltration. In nodal lymphomas, 43.2% were stage III. According to International Prognostic Index (IPI) 41.7% of patients was low risk, 39%were intermediate risk and 16.7% were high risk. 31/37 (83.8%) received Rituximab as first line. The mean number of cycles was 6. Overall response rate was 89.2%, 64.9% of patients had complete response and 24.3% had partial response. No statistical difference in overall response rate between aggressive NHL and low grade lymphoma were noticed(p=0.2). In extra nodal NHL 87% were stage I. All received Rituximab as first line. Overall response rate was 82.6%, with 52.2% complete response and 30.4% partial response.

Conclusion: Our results show that Rituximab had high response rate comparable with international results. More time is needed to assess event free survival and overall survival.

Introduction

Non-Hodgkin's lymphoma (NHL) is the most common hematological cancer in adults. (1, 2). NHL encompasses a heterogeneous group of lymphomas that have been classified in various ways. In 1995, the World Health Organization developed a classification that included a combination of morphology, immunotyping, genetic features, and clinical syndromes. The goal was to define disease entities of B cells, T cells, and natural killer (NK) cells that pathologists could recognize and had clinical relevance . Lymphomas were further subdivided into categories based on their behavior {indolent, aggressive or highly aggressive). (3.4)

B-cell lymphomas account for about 85% of all NHL diagnosis .(5)

NHL are grouped as either indolent subtypes whish has prolonged median survival but considered incurable or aggressive subtypes whish has rapid growth with potential intent for cure.

Conventional method of treatment including chemotherapy and radiotherapy. Cell surface proteins such as CD19, CD20, and CD 22 are highly expressed on B- cell lymphoma and represent key potential targets for treatment. Antibody therapy directed against CD 20 has had the most important clinical impact to date.

Rituximab is a chimeric antibody directed against the CD20 antigen which is a 297 amino acid phosphoprotein (33-35KD) found on the surface of B cells. CD 20 is highly expressed on the surface of B cells but not on stem cells, Pro-B cells, plasma cells or other cell types. It is the first monoclonal antibody licensed for treatment of NHL; it has been approved by Food and Drug Administration (FDA) in USA in Nov. 1997. CD 20 is a transmembrane surface antigens expressed only by B-cell precursors and mature B cell. It is involved in the regulation of B-lymphocyte growth and differentiation. CD20 is expressed on more than 85% of B cell in NHL but not on stem cells or normal mature plasma cells or other normal tissues, and lost when normal B cells differentiate into antibody secreting plasma cells. (6,7).

CD20 is present on malignant plasma cells in 20 % of patients with Multiple Myeloma and up to 50% of patients with plasma cell leukemia and 75%-100% of patients with Waldenstrom's macroglobulinaemia (8).

CD20 positive cell can totally be eradicated without causing specific toxicity because normal B cell will re-emerge following differentiation from stem cells. CD20 is not internalized after binding to antibody, then anti CD20 antibody initiate immune response and apoptosis.

Rituximab is genetically engineered human/mouse chimeric monoclonal antibody, that is specific for CD20 B cell surface antigen. (9) Rituximab consists of human IgG1, kappa constant region with variable region isolated from murine anti- CD20 antibody. It consists of two heavy chains and two light chains with molecular weight of 145 KD. Rituximab has low potential for immunogenicity, because the majority of the molecules are of human origin. Rituximab effectively reduces the circulating B-cell count in lymphoma patients by complement medicated cytotoxicity, Antibody-dependent cellular cytotoxicity (ADCC) and induction of apoptosis. Rituximab binds directly the C1q complement component, initiating complement mediated lysis of circulated B cell (9). Rituximab binds strongly to FC receptor on Macrophage and natural killer cells inducing ADCC (10). Rituximab induces apoptosis. (10) Recent studies suggest that complement - dependant cytotoxicity may be more important than ADCC. (11) Rituximab may be effective in patients who have failed to respond to chemotherapy or who have relapsed after chemotherapy. Regarding toxicity, no significant toxicological effects were observed at various doses and schedules. Only B cell depletion was observed and time to recovery needs 3 months with partial recovery most commonly occurring after 4-8 weeks.

More than 300,000 patients worldwide have been treated with rituximab. It is a well tolerated treatment. Rituximab administration is not associated with severe hematological or other adverse events, commonly seen with chemotherapy. Patients may experience infusion related reaction like fever and chills during the first 2 hour of the first infusion, these decrease substantially with subsequent infusions. Other side effects include, dyspnea, often with bronchospasm and hypoxia, flushing, angioedema, nausea, urticarial, rash, headache, throat irritation, rhinitis, vomiting and tumor pain. In 10% of patients these events are accompanied by hypotension. Tumor lysis syndrome has also been reported following rituximab administration. (12)

Despite profound B cell depletion, the incidence of infection is not increased compared with chemotherapy alone. The (GELA -LNH-98.5) study, showed no additional toxicity with chemotherapy (13)

Patients and method

Retrospective non-randomized study includes all patients registered as Non-Hodgkin Lymphoma in oncology clinic in Tripoli Medical Center .88 patients were registered in the period between Jan 2011 and Dec. 2013. 60 patients with CD20 positive B cell Non-Hodgkin Lymphoma proved by immunohistochemistry had received Rituximab with chemotherapy.

Study includes patient's characteristics as sex, age, extranodal or nodal involvement, stages of disease at diagnosis according to Ann Arbor staging System, and international Prognostic Index (age, LDH, more than 2 extranodal involvements, advanced stages as III, IV.). Histopathology depends on cell morphology and immune stain according WHO classification system.

Rituximab was given to CD20 positive B cell NHL as 375 mg/ m^2 every 3 weeks for 6-8 cycles with chemotherapy as CHOP or CVP protocol. CHOP represent cyclophos-phamide, Adrimycin, Vincristine and predinsolone and CVP protocol stand for cyclophosphamide, vincrestine and predinsolone as first line treatment.

Response was assessed by clinical examination and CT scan chest and abdomen as complete response or partial response. Disease free survival and overall survival was studied and we need more time to assess these variable.

Statistical analysis: data was analyzed using SPSS computer software package, and Kaplan Meier curves used for survival analysis.

Results

88 patients were diagnosed as Non-Hodgkin lymphoma in the period between Jan 2011-Dec 2013. Table (1) shows patients characteristics. Median age was (56.5 years, SD± 16.3), and mean age was 55.5 years with standard error of 2.287. 62/88 (70%) were high grade NHL. 19/88 (21.3%) were low grade NHL as follicular, MALT cell, and small cell. 5/88 (5.7%) were

Table 1. Patients characteristics

	Nodal	Extranodal
Number of patients	37	23
Median age (years)	57	54
Male :female ratio	1:1.5	1:1.1
Sweating	32.4%	8.7%
Fever	37.8%	4.3%
Wight loss	32.4%	39.1%
Itching	10.8%	-
Peripheral lymphadenopathy	34/37 (91.9%)	Gastric 56.5% Bone 13% Thyroid 4.3% Nasopharynx 4.3%
Mediastinal lymphadenopathy	10/37 (27%)	Small intestine 4.3% Anorectal 4.3% Soft tissue 8.6% 4.3%
Bulky mediastinum	10/37 (27%)	-
Splenomegaly	4/37 (10.8%)	-
Hepatomegaly	6/37 (16.2%)	-
Tonsil involvement	2/37 (5.4%)	-
Leukocytosis	7/37 (18.9%)	3/23 (13%)
Median hemoglobin concentration	11.5 g/dl	11.8 g/dl
ESR> 50mm/hour	7/37 (18.9%)	6/23 (26%)
LDH high	19/37 (51.4%)	7/23 (30.7%)
Bone marrow involvement	18.9%	4.3%
Stages according to Ann Arbor		
Stage I a	13.5%	56.5%
Ib	5.4%	30.4%
IIa	8.1%	4.3%
IIb	5.4%	4.3%
IIIa	18.9%	-
IIIb	24.3%	
IVa	8.1%	4.3%
IVb	13.5%	4.3%
International prognostic index		
*low risk	41.7%	
*intermediate risk	39%	
*high risk	16.7%	
Rituximab with chemotherapy as first line	31/37 (83.8%)	23/23
Rituximab with chemotherapy as second line	6+2 (who relapsed after failure of first line)	
Overall response rate	89.2%	19/23(82.6%)
*Complete response	64.8%	52.2%
*Partial response	24.4%	30.4%
Death	8/37(21.6%) 2/8 (25%) unrelated cause	6/23 (26%)

T cell lymphomas. 70/88 (79.5%) are CD20 positive B cell type. 60/70 (85.7%) patients with CD20 positive B cell received Rituximab as first line with chemotherapy or after relapse after chemotherapy. 6/70 (8.6%) received chemotherapy only, 4/70 (5.7%) were unfit to receive any treatment. The 60 patients who were CD20 positive who received Rituximab, 26/60 (43.3%) were male, and 34/60 (56.7%) were female. 37/60 (61.7%) had nodal involvement and 23/60 (38.3%) had extra nodal involvement. Among patients with nodal involvement (37/60), the median age was 57 years and mean age was 54.88 years. 22/37(59.5%) were female and 15/37(40.5%) were males.

The main symptoms were as following: 32.4% had sweating, 37.8% had fever, 32.4% had history of weight loss, and 10.8% had itching. 34/37 (91.9%) present with peripheral lymphadenopathy, 10/37 (27%) had mediastinal lymphadenopathy with 4/10 (40%) bulky mediastinum. 4/37(10.8%) had splenomegaly, 6/37 (16.2%) had hepatomegaly and 2/37 (5.4%) had tonsils involvement. 7/37 (18.9%) had leukocytosis, median hemoglobin concentration was 11.5 g/dl, 7/37 (18.9%) had high ESR > 50 mm/1st hour, and LDH were high in 19/37 (51.4%).

27/37 (73%) had aggressive lymphoma high grade NHL. 22/27 (81.4%) had diffuse large cell B cell type. 10/37 (27%) had indolent lymphoma low grade NHL, 3/10 (30%) had follicular subtype.

According to Ann Arbor staging system; stages of patients were as follows Ia 13.5%, Ib 5.4%, IIa 8.1%, IIb 5.4%, IIIa 18.9%, IIIb 24.3%, Iva 8.1%, IVb 13.5%.

According to International Prognostic Index IPI, 41.7% were low risk, 39% were intermediate risk and 16.7% were high risk. 6/37 (18.9%) had positive bone marrow.

31/37 (83.8%) received rituximab as first line with chemotherapy as CHOP Cyclophosphamide, Vincristine, Adriamycin and prednisolone or CVP Cyclophosphamide, Vincristine, and prednisolone with mean Number of cycles was 6.

Overall response rate (ORR) was 89.2%, with complete response in 64.8% and 24.3% had partial response. Among responders 2 patients relapsed.

8 patients received rituximab as second line 7/8 (87.5%) had response, 3/8 (37.5%) had complete response, and 4/8 (50%) had partial response.

No statistical difference in overall response rate between aggressive non-Hodgkin lymphoma and low grade Non Hodgkin Lymphoma p=0.2. 8/37(21.6%) patients died during follow up, 2 had unrelated death.

Among extra anodal lymphomas, 23 patients with mean and median age 54 years.12/23 (52.2%) were female and 11/23 (47.8%) were males.

Main symptoms were as following: 2/23 (8.7%) had sweating, 1/23 (4.3%) had fever, and 10/23(39.1%) had history of weight loss.

Gastric NHL was the most common extra nodal involvement in 13/23(56.5%), bone in 3/23 (13%), thyroid in 2/23(8.7%), nasopharynx in 1/23 (4.3%), small intestine in1/23(4.3%), anorectal in 1/23(4.3%), and 2/23(8.6%) had soft tissue lymphoma.

Regarding laboratory investigation mean hemoglobin was 11.8g/dl, 3/23 (13%) had leukocytosis, high ESR >50 mm/hour in 6/23 (26%), and 7/23 (30.4%) had high LDH.

Histological examination was 21/23(91.3%) has aggressive large cell B cell lymphoma, 2/23(8.7%) had low grade NHL of MALToma type.

According to Ann Arbor staging system; stages of patients were as following Iea 56.5%, Ieb 30.4%, IIea 4.3%, IIeb 4.3%, IVea 4.3%, IVeb 4.3%.

Among these patients 1/23 (4.3%) had bone marrow infiltration.

Rituximab was given in combination with chemotherapy as CHOP or CVP for all patients with extranodal lymphoma.

Overall response rate was 19/23 (82.6%), with complete response in 52.2% and partial response in 30.4%. Among responders 2 patients had relapse. During follow up 6 patients had died.

Progression free survival among all treated 60 patients (nodal and extranodal) at 3 years was 60% shown in Figure (1). Overall survival at 5 years was 40% Figure (2).

Discussion

Non-Hodgkin's lymphoma is a composite lymphoid malignancy with increased annual rate of 4% to 7% over the last 20 years in both USA and Europe (14)

Low grade Non-Hodgkin lymphoma accounts approximately 40% of the incidence of NHL in the United State. While patients with intermediate and high grade are potentially curable with combination chemotherapy, low grade Non-Hodgkin's lymphoma are still considered to be essentially incurable with standard therapy, they respond to treatment but follows a course of recurrent relapse and shorter remission. Median survival for low grade lymphoma is 6.2 years and 5 years from time of first relapse.
Diffuse large B cell Lymphoma is the most frequent, represent-

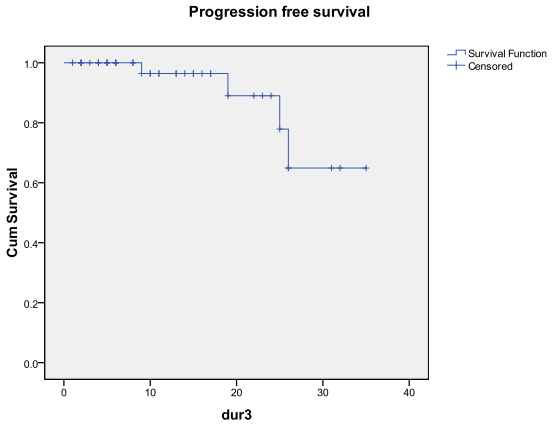

Figure 1. Overall progression free survival among all patients with NHL.

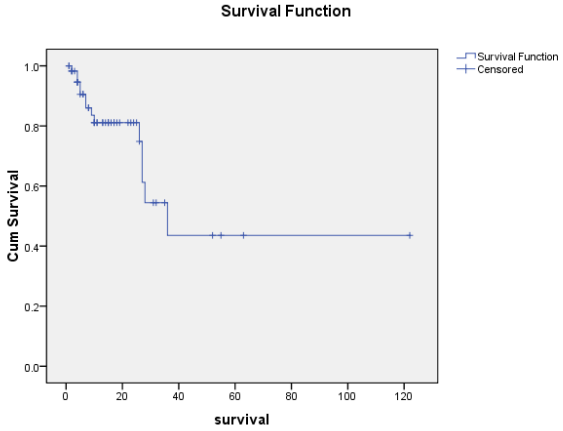

Figure 2. Overall survival among all treated patients with NHL

ing 40% of all lymphomas.

For more than 25 years, CHOP has been the standard treatment of aggressive NHL but less than 50% of patients were cured.

Vose et al. conducted a phase 2 study of Rituximab with CHOP chemotherapy in 33 previously untreated patients with advanced stage aggressive B cell lymphoma .The ORR was 94%; 61% of patients had complete response and 33% had partial response. (15).

Eight cycles of Rituximab and CHOP are now the standard first line treatment for patients between 60-80 years with aggressive NHL (previously untreated) based on The Groupe d'Etude des lymphomas de L'dulte (GELA.LNH-98.5) study (16) .

Rituximab is given in 375 mg/m2 on day 1 in each of eight cycles of chemotherapy every 3 weeks, the result were as follow: overall response rate was 63% in CHOP arm and 75% in CHOP and Rituximab (p=.005).

Overall survival was as 57 months in CHOP arm vs. 70 months in CHOP and Rituximab arm. p= (0.007).(17)

Subsequent analysis at 3 and 4 years follow- up confirmed that the significant survival advantage for Rituximab and CHOP was maintained.
The addition of rituximab to CHOP increases the number of patients being cured of their disease. (17)

According to International Prognostic Index (IPI), rituximab &CHOP significantly improved response rate, event free survival, and overall survival rate compared with CHOP alone in low risk as well as high risk patients. (17).

Based on GELA-LNH 98.5 trial (British-Colombia cancer Agency) implemented a new policy recommending that 8 dose of rituximab &CHOP should be given to all newly diagnosed patients with aggressive NHL (18).

Indolent type NHL follows a chronic relapsing and remitting course and remains incurable with chemotherapy. Thus, while the disease is responsive to conventional chemotherapy, no chemotherapy regimens have an impact on overall survival. Many patients with asymptomatic diseases may not be treated until their disease progresses, without any detrimental effect on survival (19).

One of the first clinical trials of Rituximab plus chemotherapy was a phase II study (20), which used Rituximab plus CHOP chemotherapy, which showed complete response in 58% and partial response in 42%, and median time to progression was more than 7 years, then two large prospective phase III randomized trials have confirmed that addition of rituximab to chemotherapy yielded major improvement in overall response, complete response rate, and progression free survival.

In Marcus et al study (21), 321 patients with advanced follicular lymphoma were treated with 8 cycles of CVP (Cyclophosphamide, Vincristine and prednisolone) plus Rituximab. The primary end point was time to treatment failure .At median follow- up of 18 months, time to treatment failure was significantly longer for patients treated with Rituximab plus CVP compared with CVP alone (26 months Vs 7 months P <0.0001).

Patients with Low grade Non-Hodgkin's Lymphoma treated with Rituximab plus CHOP Chemotherapy showed prolonged clinical and molecular remission.
In one study, 9 years follow- up of 38 patients with NHL

previously untreated were included. Overall response rate was 100%. 87% of patients achieved a complete response. The median time to progression was 82.3 months. (22).

Marcus et al 2005 (23) showed that overall and complete response rate were (81%, and 41%) in R-CVP arm versus (57% and 10%) in CVP arm (p=0.0001). Median follow- up of 30 months, median time to treatment failure was 27 months in patients receiving R - CVP and 7 month in patients receiving CVP alone .The addition of rituximab to CVP significantly improved the clinical outcome in patients with previously untreated advanced follicular Lymphoma, with- out increased toxicity.

Another large randomized trial conducted by the German low grade study Group has compared rituximab plus CHOP with CHOP alone in previously untreated Follicular lymphoma patients which showed increased time to treatment failure, improvement in progression free survival and overall survival in the rituximab plus CHOP arm (24).

Regarding our patients, 54 patients had received rituximab as first line with either CHOP or CVP ,31 patient with nodal involvement and 23 patients with extranodal lymphoma. Overall response rate was 85%, complete response in 58% and partial response in 27%

Conclusion

Rituximab has changed the treatment paradigms and outcomes for all CD20+ NHL and represents the most noteworthy advance in lymphoma treatment over the past decade. In patients with NHL ,the addition of rituximab to standard treatment significantly enhanced response to therapy and overall outcomes.

Rituximab is currently approved for treatment of relapsed and refractory indolent lymphoma as single agent and in combination with chemotherapy, and approved in patients with aggressive lymphoma with chemotherapy in previously treated and untreated patients in both nodal and extranodal sites.

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