Results of treatment of 20 Iraqi Patients with Newly Diagnosed High and Intermediate grade Non-Hodgkin's Lymphoma with VACOP-B

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Abstract

Background: CHOP regimen was the standard treatment for patients with diffuse large and mixed cells Non-Hodgkin's lymphoma (NHL) even in comparison with second and third generation regimen. Recently Rituximab –CHOP is considered the standard treatment for aggressive B-cell NHL while CHOP (alone) is so for aggressive T-cell NHL, yet more than one study investigates another regimen which is VACOP-B and some showed its superiority over CHOP. Prior to the introduction of Rituximab, we used VACOP-B in the treatment of high &intermediate grade NHL in adult Iraqi patients as an alternative to CHOP.

Patients and Methods: We performed a prospective analysis of 20 adult patients who, between April 2000 and October2005, received VACOP-B chemotherapy for high and intermediate grade NHL. The weekly regimen consisted of: doxorubicin50 mg/m^2 i.v. weeks 1,3,5,7,9,11; cyclophosphamide350 mg/m^2 i.v. weeks 1, 5, 9; etoposide 100mg/m^2iv, weeks 3,7,11; vincristine1.4 mg/m^2 i.v. (2 mg max.) weeks 2, 4, 6, 8, 10;bleomycin 10 mg/m^2 i.v.(max. 15 mg) weeks 2,4, 6,8, 10; methotrexate12.5 mg intratheical was given in selected patients.; prednisolone 60mg p.o.daily for 2 weeks, reduced to 60 mg every other day for 10weeks.The patients treated were aged 25-50 years, 8(40%) had high grade (Working Formulation)NHL; 12 (60%) had intermediate grade NHL;seventeen patients(85%) had Stage III/IV disease; and 3 (15%) had stage II,bone marrow involvement seen in 3(15%)patients .patients distribution regarding age adjusted international prognostic index(aaIPI)was 8(40%)with aaIPI 0,1and 12(60%)with 2,3. Follow-up time from completion of VACOP-B chemotherapy ranged from 6 months to 40 months (median 22).

Results: VACOP-B induced a complete response (CR) and partial response (PR) in 70% and 15% respectively, whilst one patient had no response to treatment and died due to progression of the disease, 2 patients died due to treatment related toxicity. The three year disease free survival (DFS) was 78%, where 4 patients relapsed, one of them in the central nervous system. This study showed 3-year overall survival (OS) 100% for those with a IPI 0-1and 48% for those with aa IPI 2-3. Tolerance to treatment was measured by WHO toxicity scores. The hemoglobin (Hb) toxicity median score for all patients was grade 1 (Hb 9.5-10.9 g/dl), and the white cell count (WCC), toxicity score was grade 2(WCC 2.0-2.9 x 109/1). No platelet toxicity was observed. Ten per cent of patients suffered grade 3 severity infections requiring antibiotics and there was two treatment related death.

Conclusions: VACOP-B chemotherapy is an effective regimen for high and intermediate grade NHL, with an encouraging result in patients with aaIPI 0, 1. although chemotherapy was given weekly, the tolerance to treatment was acceptable. Studies comparing VACOP-B vs. CHOP chemotherapy to decide the exact role of the first in treating high grade &intermediate grade NHL, in the absence of Rituximab, are still needed.

Keywords: VACOP-B; Non-Hodgkin's lymphoma.

Introduction:

Although some patients with intermediate-grade or high-grade (aggressive) Non-Hodgkin's lymphoma (NHL) are cured by combination chemotherapy, the remainder are not cured and ultimately die of their disease. This difference in prognosis exists even in same category of WHO/ REAL classification. The Ann Arbor staging system does not consistently distinguish between patients with different long-term prognosis. (1)

**Collage of medicine-Baghdad University/Medical city complex &Haemtology Unite –Baghdad Teaching Hosp./Medical City Complex* In 1993, the International N.H.L prognostic factors group conducted a study where adults with aggressive Non-Hodgkin's lymphoma from16 institutions and cooperative groups were evaluated for clinical features predictive of overall survival and relapse-free survival. They found that age, tumor stage, serum lactate dehydrogenase concentration, performance status, and number of extra nodal disease sites identified four risk groups(0,1,2,3,4) with predicted Five- years survival rates of 73 percent, 51 percent, 43 percent, and 26percent. In patients 60 or younger, an age-adjusted model(table 1) based on tumor stage, lactate dehydrogenase level

and performance status identified four risk groups with predicted five-year survival rates of 83 percent, 69percent, 46 percent, and 32 percent. In both models the increased risk of death was due to both a lower rate of complete responses and a higher rate of relapse from complete response. These two indices ,called the international prognostic index(IPI) and the age-adjusted international prognostic index (aaIPI),both were significantly more accurate than the Ann Arbor classification in predicting long-term survival.(1)

Many advances have been made in the treatment of NHL lymphoma over the past four decades. The potential for cure was realized with the use of combined drug regimens such as COP or CVP(cylcophosphamide, vincristine, prednisolone),which produced long term disease free survival in just under 20% of patients with large cell non-Hodgkin's lymphoma (NHL) (2).This paved the way for the use of four-drug regimens, CHOP (3)and C-MOPP (4) with higher response rates.

As a result of the discoveries in the late 1970s, a second generation of regimens arose. Three-week cycles were used, often with more drugs. Marrow sparing agents such as bleomycin and vincristine were incorporated into the regimens. More recently, a third generation of regimens has been introduced. These make use of therapeutic maneuvers such as briefer, more intense schedules dose escalation, and the further use of marrow sparing, cycle active, non-cross resistant agents (Goldie-Coldman hypothesis (10)

In general, these regimens rely on the use of larger numbers of agents given in more intense schedules to combat the rapid cell cycling times and high growth fractions found in malignant lymphoma. Higher response rates have been claimed (84% for MACOPB; 80% for ProMACE-CytaBOM). However, long term disease free survival remains lower, whilst appreciable toxicity exists and must be considered when selecting the appropriate regimen for an elderly patient (11). In 1991,Susan E.O Reilly,et al published a study where108 patients were enrolled on a modification of MACOP-B calledVACOP-B (etoposide, oxorubicin,cyclophosphamide,vincristine,prednisolone,bleomycin)(7)the complete remission rate was 81%,and the toxic death rate lower, at 3%(6% in MACOP-B).The overall survival at 3 years was 60%&it was not statistically different from that of MACOP-B,not only that,but the incidence of moderate and severe side effects were much lower with VACOP-B(12).

Clinical trials comparing CHOP versus m-BACOD, CHOPvs ProMACECYtaBOM and CHOP vs MACOP-B reached similar conclusions. These results along with the fact that CHOP was cheaper and easier to administer than the other regimens, established CHOP as the standard therapy throughout the world (13). In 2005, A.Olivieri, et al. published the long term results of a trial, designed to evaluate the usefulness ofVACOP-B followed by high-dose therapy (HDT) with autologous stem cell transplantation as front-line treatment in different subsets of aggressive NHL. Among 223 patients aged 15–60 years with aggressive, advanced stage NHL, 106 patients were randomized to VACOP-B for 12 weeks (plus HDS/HDT in case of persistent disease) (arm A), and 117 patients to VACOP-B for 8 weeks plus upfront HDS/HDT (arm B). According to the intention-to-treat analysis, the complete response rate was 75% for arm A and 72.6% for arm B. With a median follow-up of 62 months there was no difference in 7-year probability of survival (60% and 57.8%; $P = 0.5$), disease-free survival (DFS) (62% and 71%; $P = 0.2$) and progression-free survival (PFS) (44.9% and 40.9%; $P = 0.7$) between the two arms. After this result A.Olivieri, et al believed that in patients under 60 years old, HDS/HDT should be used in case of persistent disease after front-line therapy. The current availability of rituximab for treating patients with CD20+ diffuse large B-cell lymphoma and the superiority of the association CHOP–rituximab versus CHOP alone in older patients ,suggest that it would be of interest to evaluate the opportunity of supplementing the HDS/HDT strategy with rituximab in younger patients; indeed the very promising results claimed also in young patients suggest the possibility of comparing the two strategies (CHOP-like plus rituximab versus HDS/HDT plus rituximab)(14). We report on a group of 20 patients under 50 years old who received VACOP-B as first line therapy for high &intermediate grade NHL. Response to treatment and toxicity recorded.

Patients and methods:

This study was conducted in Baghdad teaching hospital between April 2000 till October, 2005. Patients were eligible if they were below 60 years old. Diagnosis was made by excisional lymph node biopsy in the majority of patients (15 patients), the other patients were diagnosed by bone marrow biopsy (two),after laprotomy(two) and after thoracotomy (one). The entire specimens had been evaluated by an expert histopathologist. Then thorough investigations were done for staging and evaluation of the cardiac, liver and renal function. Bone morrow aspirate and biopsy was done to all patients. CT scan and MRI of the chest and abdomen were not available to all patients before treatment, but all of them had chest x-ray , abdominal and pelvic U/S .Serum LDH was done for all patients; an interview was conducted with every patient and / or his family. Disease nature, fate without treatment and with treatment and the risk of treatment, all these topics were discussed with them then a written consent was included in the case sheet.Age adjusted IPI was used since all the patients are below 60 years and it is showed in details in table (1).VACOP-B as described by O'Reilly etal (12)was started as an inpatient for the first dose then as an outpatient. Table (2) shows the treatment schedule.

Before each dose CBP & ESR, blood biochemistry and liver function tests were done. Treatment was delayed if the neutrophil count below $1x10^9$ /L or the total WBC < 2.5 $x10^9$/L for doxorubicin, cyclophosphamide or etoposide but neutrophil count of 0.5x10/L or WBC $1.5x10^9$/L were accepted for vincristine and bleomycin. Neupogen (G - CSF) was given when available in case of neutropenia. In serious infection (such as chest, diarrhea, extensive herpes zoster), we delayed the treatment, even with normal count of WBC. E.C.G. & Echo was done if there was palpitation or shortness of breath. Pulmonary function test was done only if there was shortness of breath.Three patients had received intrathecal MTX 12mg; 2 of them had immunoblastic lymphoma with high IPI and the 3rd patient had involvement of the para nasal sinus. It started after the fifth dose as 5 doses weekly, IT injections given. All adverse events as reported by the patient or observed by the investigator were collected and distributed in predefined categories. An adverse event was defined as any adverse change from the patients' base- line condition, whether it was considered related to treatment or not (15). Each event was graded according to the National criteria grading system (16). Response assessment **:** The patients had their first re-evaluation after the 4th dose then after the 8th in addition to the final evaluation in the last dose and 4 weeks later. Each evaluation includes CBP, ESR, chest X-ray, abd u/s, LDH. While CT scans (chest and / or abdomen) were done after the last dose only with the bone morrow aspirate and biopsy. The response was assessed according to standard criteria that were developed in 1998 by an International workshop of lymphoma investigators (17). Follow up:- In the first year after CR, monthly follow up was scheduled then every 3 months in the 2nd year, then twice per year in the 3rd year and later. National cancer institute (NCI) common toxicity criteria was used to score levels of myelosuppression (Hb, WCC and platelet toxicity), stomatitis, nausea, neurotoxicity, and degree o f infection. The number of weeks of treatment delay and the number of units of blood transfused were recorded.

Statistical analysis: The analysis was performed using SPSS, virgin 9, three years. Overall survival (OS) was calculated by the Kaplan – Meier method from the date of starting therapy until last contact or death from any cause. Three year progressive free survival (PFS) was calculated for patients who achieved a response after VACOP-B to the date of last contact or to relapse or death.Three years Disease free survival (DFS) was calculated for those who achieved complete remission (CR) from the response till death or relapse. OS calculated for those with aaIPI 0-1 and those with aaIPI2, 3. Log – rank test was used to compare OS of aaIPI 0, 1 & aaIPI 2, 3. A multivariate COX regression analysis was performed to assess the effect of pretreatment prognostic factors (sex, no. of extranodel sites.B symptoms , LDH performance status & stage) on the result of treatment. A P value < 0.05 was considered indicative of statistical significance difference.

Results:

The patients treated were aged 25-50 years, 8(40%) had high grade (Working Formulation) NHL; 12 (60%) had intermediate grade NHL;17(85) had Stage III/IV disease; and 3 (15%) had stage II, Bone marrow involvement was seen in 3(15%)patients. Patients distribution regarding age adjusted international prognostic index(aaIPI)was 8(40%)with aaIPI 0,1and 12(60%)with 2,3. Table (2) shows the descriptions of the patients VACOP-B induced a complete response (CR) and partial response (PR) in 70% and 15% respectively, whilst one patient had no response to treatment and died due to progression of the disease table (3). Two patients died due to treatment related toxicity. Our study showed 3-years overall survival (OS) was67% (fig 1) while it is 100% for those with aa IPI 0-1 and 48% for those with aa IPI 2-3 (P value<0.01), (Fig. 2& 3 respectively) .The three years disease free survival (DFS) was 78%(fig.4), where 4 patients relapsed, one of them in the central nervous system, three months after the end of treatment. The other three patients relapsed within three months. Multivariate analysis of the effect of pretreatment factors on remission induction result showed that LDH (> normal) was associated with lower remission rate (P=0.03).

Toxicity: The fall in Hb was usually minimal but 38% did experience grade II toxicity (Hb 8.0.9.4 g/dl) and10% required transfusion of three units of blood. The median WCC toxicity score was 2 (WCC 2.0-2.9x 10^9/1) and 23% suffered from moderate to major infections requiring intravenous antibiotics. No platelet toxicity was observed. Neurosensory, nausea and stomatitis median scores were 0 (Table 4). The median number of weeks, that treatment was postponed, was 1 week.

Table (1) calculation of age adjusted IPI

FEATURE	SCORE 0	SCORE 1
Ann Arbor Stage	I/ II	III/ IV
Serum LDH	Normal	Elevated
Performance status	0, 1	2-4

IPI risk group	Age adjusted IPI
Low-risk	0
Low/intermediate-risk	1
High/intermediate-risk	2
High-risk	3

Table (2) VACOP-B schedule

Drug	Dose	Method	Day
Doxorubicin	50 mg/m^2/day	i.v.	Day1; weeks 1, 3, 5,7, 9,11
Cyclophosphamide	350 mg/m^2/day	i.v.	Day 1; weeks 1, 5, 9
Vincristine	1.2 mg/m^2/day(max 2mg)	i.v	Day1; weeks 2, 4, 6,8,10,12
Bleomycin	10 mg/m^2/day	i.v	Day1; weeks 2, 4, 6,8,10,12
VP 16	100 mg/m^2/day	i.v	Day 1; weeks 3, 7, 11
Prednisolone	75mg/day	p.o	Daily for 2 weeks then every other day for 10 weeks

Table (3) : characteristics of the 20 patients

CHARACTERISTIC	No. of patient (%)
Age <40 YRS. >40YRS.	 16(8%) 4(20%)
Sex Male Female	 12(60%) 8(40%)
Performance status * 0,1 > 1	 16(80%) 4(20%)
Stage Limited(I ,II) Advanced (II bulky III , IV)	 0(0%) 3(15%) 17(85%)
B- symptoms **	16(80%)
No. 4 extramarital site ≤ 1 > 1	 8(40%) 12(60%)
Bulky tumor (> 10 cm)	7(35%)
Bone marrow involvement	3(15%)
LDH ration ≤ 1 > 1	 8(40%) 12(60%)
Extra nodal site Spleen Liver GIT Max. sinus Pleurae, peritoneum	 9(45%) 9(45%) 2(10%) 1(5%) 6(30%)
Histology (WF) Intermediate grade High grade	 12(60%) 8(40%)
IPI (age adjusted) 0,1 2,3	 8(40%) 12(60%)

*** Performance states was defined according to the criteria of the ECOG**

**** B symptoms were defined as weight loss, fever and night sweets**

Table (4) : Outcome of treatment of 20 patients.

Response	**Number (%)**
Complete response	14 (70%)
Partial response	3(15%)
Death (total). *	3(15%)
Treatment related	2(10%)
Due to progression of the disease	1(5%)

***Death during treatment period**

Table (5) survival function of 20 patients treated with ACOB-P.

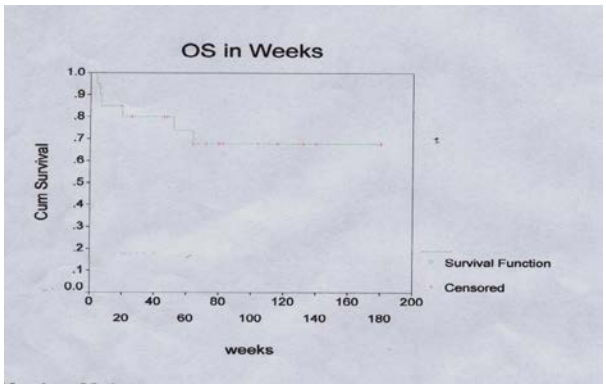
Survival function	Number of patients	percentage
3-year overall survival	20	67
3-year overall survival for a.a,IPI 0,1	8	100
3-year overall survival for a.a,IPI2,3	12	45
3-year disease free survival	20	78

Table (6) the toxicity of VACOP –B according to NCI system

Toxicity	**Incidence Of Toxicity**		
	Grade 1 or 2	Grade 3	Grade 4
Anemia	50%	15%	10%
Hemorrhage	5%	-	-
WBC	90%	20%	15%
Platelet	50%	-	10%
Infection	20%	15%	10%
Fever	20%	-	10%
Nausea &vomiting.	90%	10%	-
Stomatitis	55%	10%	-
Diarrhea	-	-	-
Arrhythmia	5%	-	-
CNS	-	-	-
Periph N.	50%	5%	-
Alopecia	-	-	-
Endocrine high Bl. sugar SE of steroid	 - 50%	 - 20%	 - -

Table (7) different Regimen and their results in related studies.

Regimen	Institution	No. of pat.	CR %	DFS % (3years)
MACOP – B	Cancer control Agency British (1985)	126	86%	58%
VACOP – B	European society (1992)	60	76%	58%
VACOP – B	Seniti G etal (1998)	61	75%	60%
VACOP – B	Present study (Baghdad Teaching Hospital)	20	70%	78%



(Fig (1): Kaplan – Meier survival curve: three years overall survival of all patients)

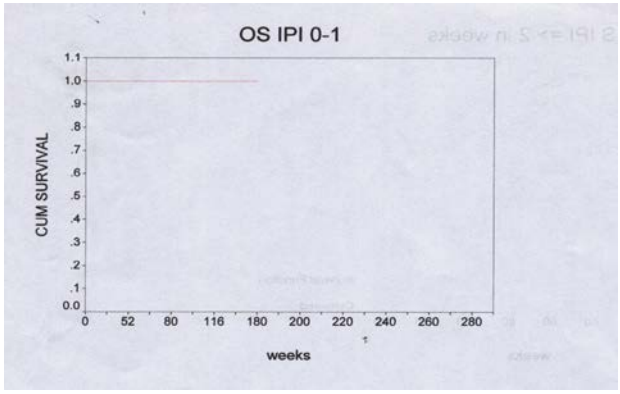


Fig. (2): Kaplan – Meier survival curve: three years overall survival of 8 patients with IPI 0,1

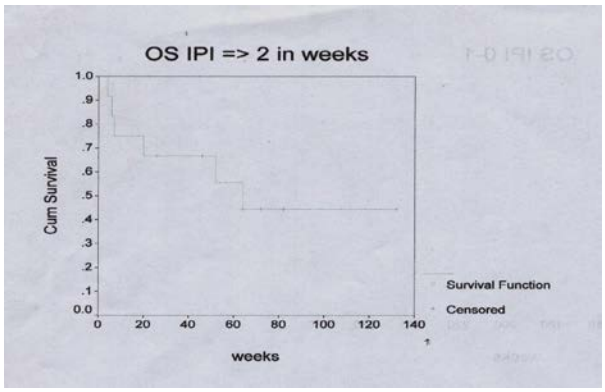


Fig. (3): Kaplan – Meier survival curve: three years overall survival of12 patient with IPI 2, 3

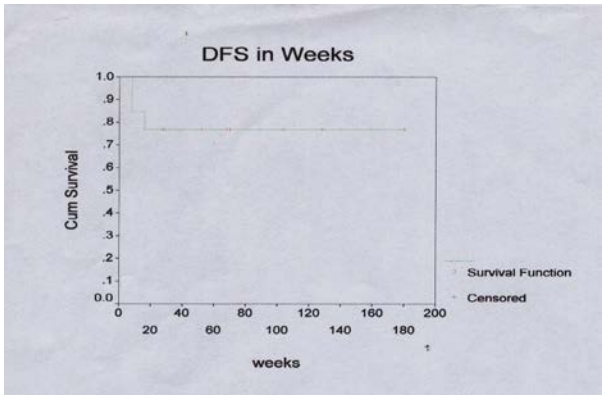


Fig. (4): Kaplan – Meier survival curve: three years disease free survival).

Discussion:

VACOP-B is a third generation regimen used in the treatment of high and intermediate grade N.H.L with a result of 76% CR & actuarial 3yrs progression free survival 40% (12,13). Phase III study conducted by SWOG and ECOG showed that there was no significant difference in term of CR and survival between VACOP-B(and other related regimen) and CHOP. (13). we have found more than one study using VACOP –B as front line treatment in intermediate & high grade N.H.L (14,18) not only that but there are Studies that showed the superiorly of VACOP –B vs. CHOP in certain types of aggressive lymphoma like in primary mediastial large cell lymphoma (18). In the current study, out of 20 patients, 14 patients (70%) had complete remission. 4 patients relapsed, 2 after 1 months (i.e. 8 weeks after stopping treatment). Review of the slides of these 2 patients by the pathologist revealed a high suspicion to be of peripheral T-cell and this goes with the large prospective trials that had indicated a worse prognosis for PTCL than DLBCL (except anaplatic large cell lymphoma of T origin)(19). The 3rd patient with high IPI 3 relapsed after 10weeks. The 4th patient who relapsed needs special mention where she was a case of intermediated grade with mixed large and small with bone marrow involvement VACOP –B was started and we were planning to start her on IT MTX but the family refused that and after 1 month the patient presented with CNS manifestation. Three patients had received IT MTX, 2 because of Bone marrow involvement and one because of paranasal involvement . (12) Klimo and Connors used both MTX (12mg) and ara-c 30 mg/ m^2 twice weekly for bone marrow involvement starting after the sixth or eighth week and with documentation of clearness of the bone marrow .(12). The four cases with relapse and the three with partial remission all of them needed second line chemotherapy & salvage therapy but three of them died before the second remission. There is obvious difference between the OS of those with aaIPI 0 – 1 & those with aa IPI 2- 3 , and this difference was established by the workers of IPI issue where they found 75% and 60% 3yrs OS for low and low intermediate (IPI 0,1,2) and 30% ,25% 3yrs OS for high and high intermediate (IPI 3,4,5) . This study report 48% 3yrs OS for IPI 2, 3, & 100% for those with IPI 0,1 and the log – rank test shows a significant difference ($P< 0.011$).

The OS of 100% in those with IPI 0, 1 indicates that such patients have limited stage N.H.L A comparison between the result of this study and similar studies using the same and different regimen cannot be made and needs a randomized prospective study.Table (5) shows a list of related studies with CR & DFS and rapid view shows higher percentage of DFS in comparison with these studies and this may be a reflection of the difference in stage and IPI rather than the modality of treatment. Susan E.O Reilly et al reported 3% mortality (12) while it is 10%in this study. The difference in the criteria of the

patients, size of the sample (108 vs.20) and the special circumstances of our country during the study period, should be considered as there were difficulties in providing adequate supportive care such as new generation antibiotics and G-CSF. The third patient died due to progression of the disease.

Conclusion:

VACOP-B chemotherapy is an effective regimen for intermediate and high grade NHLin adult, with an encouraging result in those with aaIPI 0, 1. Although chemotherapy was given weekly, the tolerance to treatment was acceptable. Studies comparing VACOP-B vs. CHOP chemotherapy to decide the exact role of VACOP-B in treating high grade &intermediate grade NHL, with or without Rituximab, are still needed.

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