Outcome of Frontline Therapy of Hodgkin's Lymphoma Patients in Baghdad Hematology Centering the Medical City

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ABSTRACT:

BACKGROUND:

Hodgkin's lymphoma is one of most curable lymphoid malignancy. Here we conducted in this study the outcome of frontline therapy in adult Hodgkin's lymphoma patients.

AIM OF STUDY:

1. To evaluate the results of first line treatment with ABVD chemotherapy protocol in patients with Hodgkin's lymphoma in this study.
2. To find predictors associated with poor outcome of first line treatment with ABVD chemotherapy protocol in patients with Hodgkin's lymphoma in this study.

METHODS:

This is a retrospective and prospective study in which information was gathered from Baghdad hematology center involving 50 patients who were diagnosed with Hodgkin's lymphoma from 1/1/ 2017 until mid of 2019 and treated with frontline therapy, ABVD chemotherapy protocol.

RESULTS:

The mean age of diagnosis was 29.6 ±12.12 year. Nodular sclerosis was the predominant subtypes constituted (62%) of patients. Advanced stage disease involved 86% of patients. At interim evaluation by imaging studying including either ultrasound and CT scan or Pet scan according to availability , complete remission, partial remission and progressive disease involving 58% , 26% and 16% of patients respectively. Two years progression free survival was 68.95%. There was a strong correlation between lymphocytopenia and progression free survival. In this study, univariate analysis showed that initial lymphocytopenia was poorly associated with chance of achieving complete remission at end of treatment.

CONCLUSION:

The outcome of ABVD in this study shows lymphocytopenia was poorly associated with complete remission at end of treatment of patients.

KEYWORDS: Hodgkin's lymphoma, frontline therapy, outcome, progression free survival.

INTRODUCTION:

Hodgkin's lymphoma was a malignant lymphoid disease.[1]. Hodgkin's lymphoma is categorized into two categories classical Hodgkin's lymphoma (95%) or nodular lymphocyte-predominant (5%).[2]

The German Hodgkin's Disease 10 trial showed that two cycles of ABVD followed by 20 Gy of involved-field radiation is the best approach in early stage favorable risk classical Hodgkin's lymphoma. [3]

Four cycles of ABVD followed by30Gy radiotherapy was considered the standard of care for unfavorable early stage Hodgkin's lymphoma and patients with advanced stage must be treated with either 6–8 cycles of ABVD or 6 cycles of escalated BEACOPP .[4]

PATIENTS AND METHODS:

This is a prospective and retrospective study of 50 patients in Baghdad Hematology Center, those who were diagnosed with Hodgkin's lymphoma from 1/1/ 2017 until mid 2019.

Inclusion criteria:

Patients newly diagnosed with Hodgkin's lymphoma, from both sexes, their age is 14 years old and above.

Exclusion criteria : Loss of follow up during treatment Data collection.

The following data were included:

- Demographic data.
- Clinical presentation and findings during clinical examination of the patients.
- Stage of disease.

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- Pathological subtypes nodular sclerosis, mixed cellularity, lymphocyte rich, lymphocyte depleted, nodular lymphocyte predominant Hodgking's lymphoma.
- Immunohistochemistery whether done including (CD15, CD30, CD20, EBV). Or not done, but the histopathological diagnosis was done by two pathologists.
- Laboratory investigations including (initial CBC, ESR, Biochemistry).
- Imagining study including either ultrasound and CT scan or PET scan according to availability at (initial presentation, interim and after completion of treatment).
- Treatment regimens whether ABVD which consists of (Doxorubicin, Bleomycin, vinblastine and dacrbazine) or BEACOPP which consists of (Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, prednisone, procabazine and GCSF).
- In this study, only two cases received BEACOPP after three cycles of ABVD.
- Radiotherapy 30Grays was divided into 15 fractions wether given or not.

Definitions In this study:

Complete remission (CR): Disappearance of all masses of any size, in lymph nodes, liver, spleen at clinical examination and imaging study, and bone marrow infiltrate cleared on repeated biopsy.

Partial remission (PR): Regression of 50% in measurable disease and no new sites, in lymph nodes, liver and spleen at clinical examination and imaging study.

progressive disease: appearance of any new lesion or increase by 50% of previously involved sites, in lymph nodes, liver and spleen at clinical examination and imaging study , and in bone marrow new or recurrent involvement.

Interim evaluation: evaluation after three cycles of chemotherapy treatment (after three months from diagnosis).

End of course evaluation: evaluation after six cycles of chemotherapy treatment (after six months from diagnosis).

PFS was defined as the time from randomization until disease progression, or relapse.

Statical analysis used in this study was:

- McNemar-Bowker Test
- Binary logistic regression analysis used to calculate the odd ratio (OR)
- Kaplan–Meier analysis
- SPSS 22.0.0 (Chicago, IL), GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA, software package used to make the statistical analysis, p value considered when appropriate to be significant if less than 0.05 .

RESULTS:

Table 1: Demographic and clinical data.

Variable	
Number	50
Age (years), mean ± SD	29.6 ± 12.2
Gender, n (%)	
Female	28 (56%)
Male	22 (44%)
Stage, n (%)	
Early (l-llA)	7 (14.0%)
Advanced (llB-Vl)	43 (86%)
IPI score, n (%)	
Low (0-2)	29 (58%)
High (3-7)	21 (42%)
Initial bulky disease, n (%)	17 (34%)
B symptoms, n (%)	43 (86%)
Histology	
Mixed cellularity (MC)	17 (34%)
Nodular sclerosis (NS)	31 (62%)
Nodular lymphocyte predominant (NLPHL)	2 (4%)
Type of therapy	
ABVD alone, n (%)	48 (96%)
BEACOPP after 3 cycles ABVD, n (%)	2 (4%)
Radiotherapy, n (%)	13 (26%)
Evaluation	
Interim PET, n (%)	27 (54%)
Interim CT, n (%)	23 (46%)
End of course PET, n (%)	33 (66%)
End of course- CT, n (%)	17 (34%)
Relapse	10 (20%)
IPI score: international prognostic index (includes: Age≥45 years, Stage 4, Hemoglobin <10.5, albumin <4, Male, WBC ≥15000/mm^3, Lymphopenia, ALC<600/mm^3. Low (0-2), high (3-7) Bulky disease:>1/3 of mediastinal diameter or lymphadenopathy >10cm.	

At interim assessment, 13 patients had partial response and at end of course, 5 of them remained in partial response, while 7 achieved complete response and one of them had progressive disease.

At interim assessment, 8 patients had progressive disease, and at end of course, 2 of them remained in progressive disease, while 3 achieved partial response and 3 of them received other line of therapy and achieved complete response...

At interim assessment, 29 patients had complete response and at end-term assessment, 27 remained in complete response status.

Thus at end of course from total fifty patients in this study, 37 patients achieved complete response, 9 patents achieved partial response and 4 patents achieved progressive disease.

At end of follow up in this study, a total of 40 patients are in complete response, 6 patients are in partial response, and 4 patients are in progressive disease , as illustrated in table (2).

Table 2:Correlation between Interim and end-term radiological findings by McNemar-Bowker Test.

End-term radiological outcomes	Interim radiological outcomes		
	Partial response (13)	Progressive disease (8)	Complete response (29)
Partial response (9)	5 (38.5%)	3 (37.5%)	1 (3.4%)
Progressive disease (4)	1 (7.7%)	2 (25.0%)	1 (3.4%)
Complete response (37)	7 (53.8%)	3 (37.5%)	27 (93.2%)
McNemar-Bowker Test = 6.500 (df = 3); p-value = 0.090			

Predictors at end of treatment (Predictors of response):
In univariate analysis; lymphopenia, initial bulky disease, both partial and progressive disease at interim appears to be poor predictors of complete response at end of treatment, while complete response at interim treatment was significant predictor of complete response, In multivariate analysis, completed remission at mid treatment becomes insignificant which indicates that this parameter is dependent predictor, as illustrated in table (3).

Table 3: Assessment of the predictors of end of treatment complete response.

	Univariate		Multivariate	
Variables	OR (95%CI)	p-value	OR (95%CI)	p-value
Lymphocyte no.<0.6* 10^9/L	0.091 (0.015-0.559)	0.010	0.224 (0.028-1.787)	0.158
Initial bulky disease	0.201 (0.052-0.772)	0.019	0.341 (0.073-1.596)	0.172
Interim treatment outcome				
Partial	Reference		Reference	
Progressive	0.857 (0.147-4.999)	0.864	0.815 (0.115-5.777)	0.838
Complete	7.429 (1.473-37.455)	0.015	4.418 (0.739-26.418)	0.103
R^2 (Cox & Snell) = 0.251 OR: odd ratio, CI: confidence interval				

Progression free survival and its predictors: Lymphopenia, presence of initial bulky disease, and progressive or partial response at mid-term assessment predict poor PFS, as illustrated in table (4)and figures(1,2,3) .

Table 4: Kaplan Meir analysis of progression free survival of various predictors.

Predictors	1 – year PFS	2 – years PFS	Median PFS (95%CI)	P value
Overall	90.0%	68.95%	28.1 (24.8-31.3)	-
Age				0.970
<30 years	89.3%	68.8%	28.1 (23.9-32.2)	
≥30 years	90.9%	71.4%	27.4 (22.7-32.0)	
Gender				0.670
Female	92.9%	69.4%	27.9 (23.9-32.1)	
Male	86.4%	71.97%	27.7 (23.2-32.1)	
Staging				0.432
Early	100%	85.7%	31.2 (26.2-36.2)	
Advanced	88.4%	63.4%	26.7 (22.9-30.4)	
IPI score				0.532
Low	93.1%	69.5%	28.7 (24.6-32.9)	
High	85.7%	69.2%	26.5 (21.7-31.4)	
Lymphocyte count				0.001 [S]
≥0.6*10^9/L	95.3%	73.4%	29.5 (26.3-32.8)	
<0.6*10^9/L	57.1%	42.9%	18.97 (10.0-27.97)	

Initial bulky disease				0.005 [S]
Negative	97.0%	79.2%	30.8 (27.4-34.2)	
Positive	76.5%	51.0%	22.4 (16.6-28.1)	
Radiotherapy				0.276
Not received	91.9%	72.7%	28.95(25.2-32.7)	
Received	84.6%	59.2%	25.0(24.8-31.3)	
Interim outcome				0.003
Progressive +partial	71.1%	58.2%	23.6 (18.5-28.7)	[S]
Complete	100%	79.6%	31.3 (28.0-34.6)	
PFS: progression free survival, CI: confidence interval				

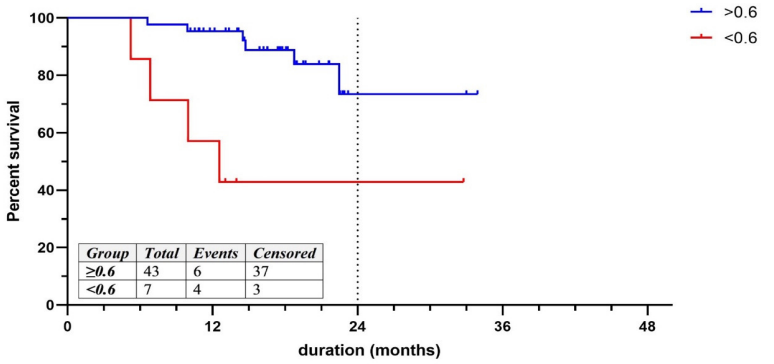

Figure 1: Progression free survival according to lymphocyte count.

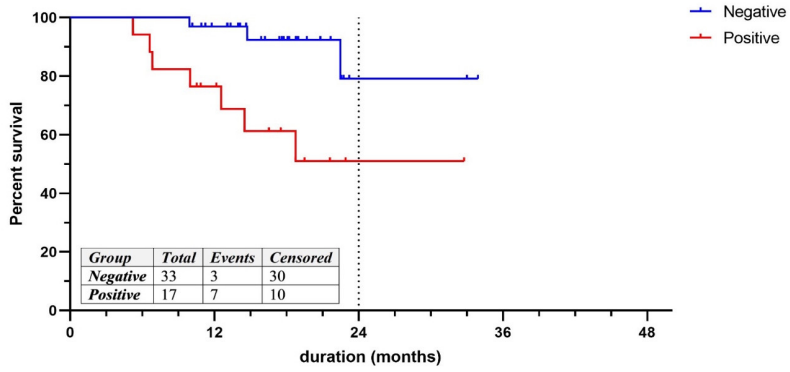

Figure 2: Progression free survival according to initial bulky disease.

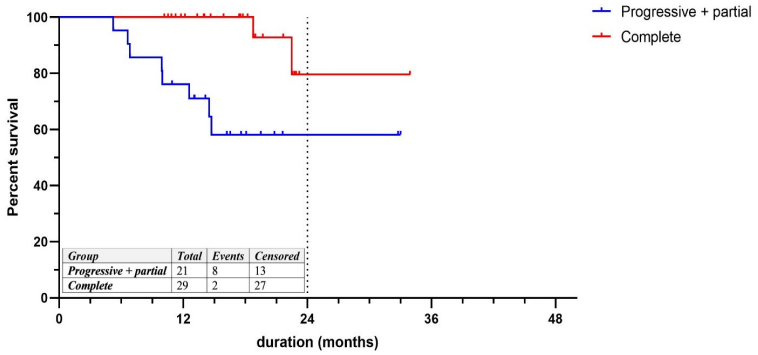

Figure 3: Progression free survival by interim evaluation. (For those with complete response versus those with partial response and those with progressive disease).

In this study, 80% of Patients had complications, grade 3 neutropenia was found in 8% of Patients. Respiratory complications including infection grade 3 was found in 6% and grade 3 pulmonary toxicity (Bleomycin induced pneumonitis) was found in 2% of patients, but gastrointestinal complications including grade2 nausea and vomiting involved 58% of patients, grade 2 diarrhea was found in 4% of patients, as shown in table(5).

Table 5: Toxicity and Complications of management of frontline patients with Hodgkin's lymphoma.

Toxicity	Grade	No.%
Nausea and vomiting	2	29 (58%)
Diarrhea	3	2 (4%)
Neutropenia	3	4(8%)
Pulmonary toxicity (Bleomycin induced pneumonitis)	3	1(2%)
Respiratory tract infection	3	3 (6%)
Cutaneous (varicella skin infection)	2	1(2%)
Overall toxicity		40 (80%)

DISCUSSION:

median age of diagnosis was 29.6 ±12.12 year which was similar to other studies in Erbil , Saudi Arabia, two studies in Italy and Malaysia in which median age was 28 years, 26years, 30years, 30 years respectively. [5,6,7,8,9]

In this study, nodular sclerosis was the predominant subtypes constituted 62%, followed by mixed cellularity 34%, and nodular lymphocyte predominant was 4% which was similar regarding nodular sclerosis and mixed cellularity to a Spanish study in which were 58.7%,33.2% respectively [10]. This study was different from an Italian study in which nodular sclerosis, mixed cellularity were 9%, 75% respectively [11].In this study, advanced stages is the predominant stage involving 86%which was similar to other study in Saudi Arabia . [5].While different in this study from other studies in France and Japan in each study advanced stage was 57%,40% respectively [12,13] . The high percentage for advanced stage in our study was explained by loss of early realization in our people about the importance when they initially observed lymph nodes swellings, delay in reaching the diagnosis by using complementary and alternative medicine, and fine needle aspiration cytology which was the first sampling procedure in developing countries, that was not sufficient for HL diagnosis. In this study, bulky disease constituted 34%, which was different from other studies in Saudi Arabia, Erbil, Spain,

France and other developed countries in which was 22%, 8.8%, 25.1%,10%, respectively [5,6,10,12].Complete remission rate at end of of follow up in this study was eighty percent which was different from other studies in SaudiArabia in which was 91%[5]. Complete remission rate at follow up end in this study was similar to other studies in western countries,developing countries and China respectively [14,15,16]. While partial response in this study at follow up end was 12% which was different from another study in France in which was 4%[12]. Also, this study was similar regarding complete remission, partial remission and progressive disease at follow up end to a study in Australia [17]. In contrast to this study in which bulky disease strongly affected progression free survival and relapse, that was different from a study in Malaysia regarding bulky disease [9]. Also, Similar to this study in which bulky affected relapse risk and progression free survival, was a Turkish study [18]. In this study, interim outcome with PET scan or CT scan had significant effect on Progression free survival which was similar to another study by Hutchings and co-workers [16].This study was similar to another study in Mayo Clinic regarding absolute lymphocyte count which was effective on progression free survival[19]. In this study, respiratory complications including infection grade 3 was 6% and grade 3 pulmonary toxicity (Bleomycin induced pneumonitis) was found in 2% of patients which was different from a French study in which was 21%,27% respectively[12].In this study, grade 2 nausea and vomiting involved nearly half of patients which was higher than a study in countries which still under development in which it was 7.6% .[20]

CONCLUSION:

- Progression free survival was 68.95% in 24 months.
- Lymphocyte count<0.6*10^9/L, initial bulky disease, partial and progressive disease at interim radiological evaluation are associated with a poorer progression free survival in Hodgkin's lymphoma patients.
- Complete remission was 80%.
- And no mortality has been registered.

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