

## Prognostic Factors of Hodgkin's Lymphoma and their Impact on Response to Chemotherapy and Survival

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### ABSTRACT

**Objective:** The aim of this study was to compare the standard prognostic factors of Hodgkin's lymphoma (HL) in relation to response to first line chemotherapy, disease free survival (DFS) and overall survival (OS).

**Patients and Methods:** The study was performed on a group of 100 adult patients diagnosed as HL and who were treated and followed-up in the years 1999 to 2001, in the Medical Oncology Department at National Cancer Institute (NCI), Cairo. The first line chemotherapy was COPP in 40%, ABVD in 35% and COPP/ABV hybrid in 25%. Patients were classified into early stage disease: Stages I, IIA and IIB without poor risk factors, n = 43 and advanced stage disease: Stages III, IV and IIB with poor risk factors, n = 57 analysis of the prognostic factors for early versus advanced-stage disease was done by univariate and multivariate regression analysis.

**Results:** Complete remission (CR) was attained in 69% of the patients after first line chemotherapy; being 87.8 % and 54.7% for early and advanced disease, respectively, ( $p=0.0001$ ). The CR rates after different chemotherapy regimens were 81.8%, 90% and 90% for the ABVD, COPP and COPP/ABV hybrid regimens in the early-disease group; respectively; in contrast to the corresponding figures of 54.5%, 50% and 61.5% in the advanced-stage group. The DFS at 4 years, was 94 %, 55% and 54.5% for the patients treated with ABVD, COPP and COPP/ABV hybrid, respectively ( $p=0.2$ ). The DFS and OS in this series of patients were 61.3% and 53.7%, being 69.8% and 70.7% for the early and 45.1% and 38.9% for the advanced-disease, respectively. The OS of the whole group was significantly related to age ( $p=0.04$ ), sex ( $p=0.005$ ), early versus advanced disease ( $p=0.0001$ ) and B symptoms ( $p=0.0006$ ).

**Conclusions:** The adequate response and DFS of the early compared to the advanced-stage disease supported the evolving role of risk adapted chemotherapy for HL. The prognostic factors proved to be of significant impact in our series. The results of this study pointed to the need for an improved treatment strategy in this potentially curable disease, especially for the advanced disease.

**Key Words:** Hodgkin's lymphoma - Prognostic factors - Chemotherapy.

### INTRODUCTION

Hodgkin's lymphoma accounts for approximately 30% of all malignant lymphoma [1]. In Egypt, the frequency of malignant Lymphoma varies between 7.8% to 12% of cancer cases according to the registries of various cancer centers [2-4] In the NCI-Egypt cancer pathology registry, the ratio of NHL to HL was 2.3: 1 and HL constituted 30.3% of all lymphoma cases [5]. A similar figure of about 30% was reported in other Egyptian series [4,6].

Hodgkin's lymphoma belong to the most curable malignancy in adults; about 80% of patients in all anatomical stages and of different histological subtypes can be cured with modern treatment strategies [1]. An appropriate therapy scheme, chosen in compliance with risk factors is important for achieving cure [7]. The scheme for dividing the patients into early (favorable) and advanced (unfavorable) cases remains a suitable instrument to tailor risk-adapted therapy according to the current knowledge.

The aim of this study is to evaluate the value of the various clinical prognostic factors for HL and to study the impact of these factors on the results of chemotherapy treatment.

### PATIENTS AND METHODS

A group of 100 adult patients who were diagnosed as Hodgkin's lymphoma were treated and followed-up in the Medical Oncology De-

partment at NCI-Cairo in the period between 1999 to 2001. The study included only the chemotherapy naïve cases and excluded the patients who didn't receive chemotherapy as their first line treatment. The prognostic factors studied are listed in table (1). In addition the factors included in the International Prognostic Score (IPS) for advanced disease were studied as well; these included HB level <10.5gm/l, TLC >15 x 10<sup>9</sup>/l, serum albumin <4gm/l and stage IV disease.

Table (1): The studied prognostic factors.

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- Age >45 year versus <45
  - Gender
  - Type of disease: early disease versus advanced disease
  - Presence of B symptoms
  - ESR > 50 or > 30 plus B symptoms versus neither
  - LDH > 500 IU/L versus < 500 IU /L
  - Extranodal involvement
  - Mediastinal involvement
  - Pathological subtypes
  - Type of chemotherapy
- 

The staging procedure was done by detailed history, careful physical examination, chest radiograph with CT chest if the radiograph is positive, abdominal and pelvic CT and bone marrow examination with core biopsy from the posterior iliac crest in stage IIB through stage IV cases. Laboratory tests including complete blood count, ESR, LDH, liver and kidney functions and serum uric acid were done before the start of treatment. According to Ann Arbor staging system, the patients were stratified into different clinical stages and then categorized into early disease including stages I, IIA and IIB without poor risk factors (large mediastinal mass and/or bulky disease >10cm) and advanced disease including stages III, IV and IIB with poor risk factors. First line chemotherapy was COPP in 40 cases, ABVD in 35 cases and COPP/ABV hybrid in 25 cases. Patients with early disease were referred to radiotherapy after 4 cycles of chemotherapy.

#### Statistical Analysis:

The studied prognostic factors in the whole group as well as in the early and advanced disease were analyzed by univariate and multivariate regression analysis. SPSS was used in

data management. Chi-square tested proportion independence. Kaplan-Meier estimated overall and disease free survival and log rank compared survival curves. For variables that showed a significance of 0.1 or less on univariate survival analysis, Cox regression multivariate analysis was done to show independent effect on survival.

## RESULTS

The median age of the patients was 37 years with a range from 18 to 74 years. Tables (2,3) showed the patients characteristics. Sixty nine percent of the patients attained complete remission to first line chemotherapy while 31% failed to attain a CR. Table (4) showed the distribution of the responding patients into the various chemotherapy regimens. There was no significant difference between the three tested regimens ( $p=0.7$ ). The CR rate was 87.8% for the early disease versus 54.7% for the advanced disease ( $p=0.001$ ). Table (5) showed the response rate in the early and advanced diseases stratified according to the chemotherapy regimens with no significant difference between the three studied regimens in both groups ( $p$  values =0.7 and 0.8; respectively).

At 4 years, the DFS of the whole group was 61.3%, while it was 69.8 and 45.1% for the early and advanced groups; respectively ( $p=0.16$ ) Fig. (1). At 4 years, the DFS was 94%, 55% and 54.5% for the patients treated by ABVD, COPP and COPP/ABV hybrid; respectively ( $p=0.2$ ) Fig. (2). The DFS of the ABVD regimen compared to that of the other two regimens showed borderline significance ( $p=0.09$ ). Fig. (3). The overall survival at 4 years was 53.7% for the whole group, while it was 70.7% and 38.9% for the early and advanced groups; respectively ( $p=0.0001$ ); Fig. (4).

Prognostic factors were studied to correlate the patients' response to first line chemotherapy. The CR rate was positively affected by stage of disease, early versus advanced ( $p=0.001$ ) and gender with significant better response in females ( $p=0.008$ ). There were trends for significant correlation between extranodal involvement and response in the early stage disease ( $p=0.09$ ) and between hypoalbuminaemia and response in the advanced stage disease ( $p=0.06$ ). The DFS of the whole group was significantly

correlated to B symptoms ( $p=0.007$ ). The DFS of the early disease was correlated to age ( $p=0.05$ ), ESR ( $p=0.04$ ) and B symptoms ( $0.03$ ). While the DFS of the advanced group was significantly correlated to gender with better results in females ( $p=0.03$ ).

In addition the response to chemotherapy and DFS were studied in relation to LDH level and pathological subtypes with no significant correlation.

The OS of the whole group was significantly correlated to age  $>45$  versus  $<45$  years ( $p=0.04$ ), sex with better response in females ( $p=0.005$ ), stage of disease early versus advanced ( $p=0.0001$ ) and the presence of B symptoms ( $p=0.006$ ). The OS of the early disease showed no significant correlation to any of the studied factors including age, ESR, presence of B symptoms and mediastinal involvement; whereas, the advanced disease showed significant correlation to age ( $p=0.04$ ) and gender ( $p=0.01$ ).

In multivariate regression analysis, the independent prognostic factors that correlated to an unfavorable response were male gender OR = 5.5 (1.4-21.8) and advanced disease OR = 4.1 (1.3-12.9). Regarding the OS, the independent prognostic factors were age  $>45$  years OR = 2.1 (1.4-4.2), male gender OR = 3 (1.2-7.4) and advanced disease OR = 3.7 (1.6-8.7). The presence of B symptoms was the only independent prognostic factor correlated to DFS with OR = 3.3 (1.3-8.7). Table (6) illustrates the independent prognostic factors that significantly influenced response to chemotherapy, DFS and OS.

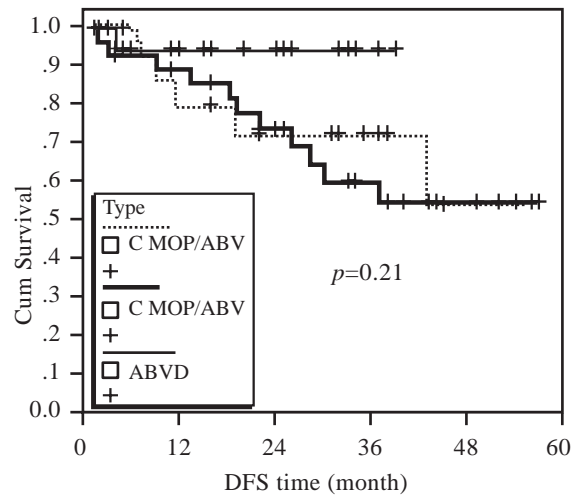


Fig. (2): DFS by chemotherapy regimen.

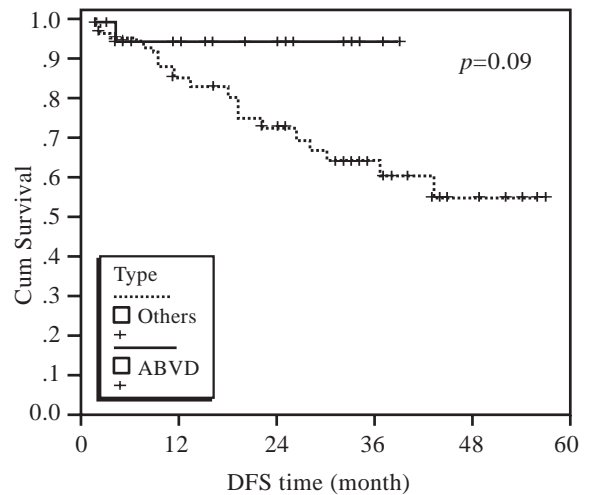


Fig. (3): DFS of ABVD regimen versus the other two regimens

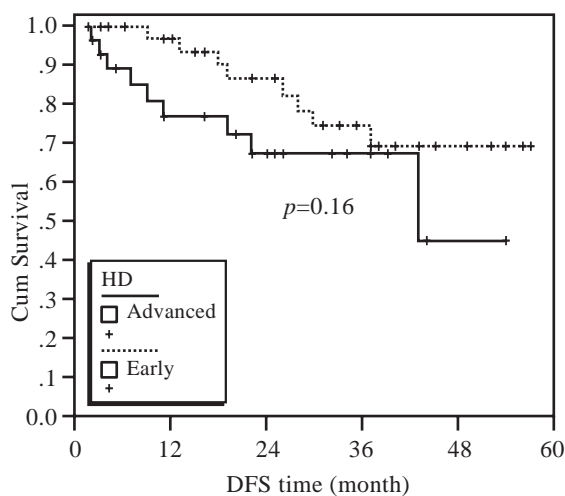


Fig. (1): DFS of early versus advanced groups.

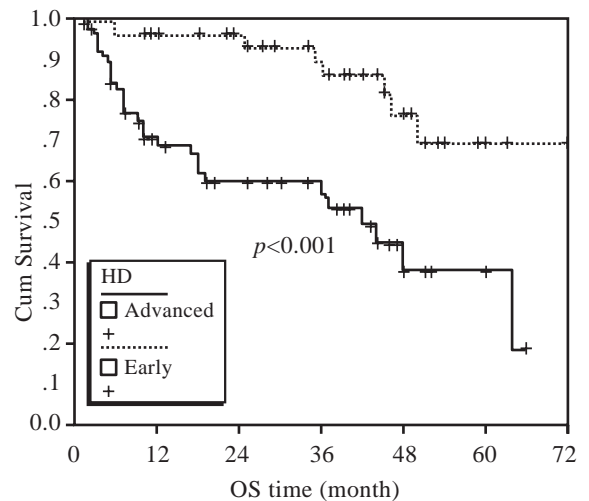


Fig. (4): O.S of early versus advanced HL.

Table (2): Patients characteristics.

Characters	%
<i>Age:</i>	
<45 years	63
>45 years	37
<i>Sex:</i>	
Males	68
Females	32
<i>P.S.:</i>	
PS I	66
PS II	30
PS III, IV	4
<i>B symptoms:</i>	
Present	31
Absent	69
<i>Pathology subtypes:</i>	
LP	20
NS	31
MC	48
LD	1
<i>Ann arbor staging:</i>	
Stage I	17
Stage II	34
Stage III	37
Stage IV	12
<i>Extranodal involvement:</i>	
Present	12
Absent	88
<i>Mediastinal involvement:</i>	
Present	28
Absent	72
<i>Type of disease:</i>	
Early	43
Advanced	57
<i>First line chemotherapy regimens:</i>	
COPP	40
ABVD	35
COPP/ABV Hybrid	25

Table (3): Laboratory values at presentation.

<i>TLC:</i>	
Median	8.5
Range	2.8-59.3 x 10 <sup>9</sup> /L
TLC >15 x 10 <sup>9</sup> /L	15%
<i>HB level:</i>	
Median	10.8 gm/dl
Range	5.4-16.5 gm/dl
HB level < 10.5 gm/dl	15%
<i>ESR:</i>	
≥50 or ≥30 + B symptoms	79.7%
Neither	20.3%
<i>LDH:</i>	
>500 IU/L	39.5%
<i>Albumin level:</i>	
<40 gm/L	64.3%

Table (4): The distribution of the responding patients into various chemotherapy regimen.

Chemotherapy regimen	Response	
	CR*	No CR
ABVD	63.6%	36.4%
COPP	71.1%	28.9%
COPP/ABV hybrid	73.9%	26.1%
Total	69%	31%

\* *p* value: NS

Table (5): The response rate of the early and advanced disease stratified according to chemotherapy regimens.

Early disease	Chemotherapy regimen	Response	
		CR*	No CR
	ABVD	81.8%	18.2%
	COPP	90%	10%
	COPP/ABV hybrid	90%	10%
	Total	87.8%	12.2%
Advanced disease	ABVD	54.5%	45.5%
	COPP	50%	50%
	COPP/ABV hybrid	61.5%	38.5%
	Total	54.7%	45.3%

\* *p* value: NS

Table (6): Independent factors that significantly influenced the response to first line therapy, DFS and OS "results of multivariate analysis".

	Unfavorable factors	O.R (95% C.I)
Response to treatment	Male gender	5.5 (1.4-21.8)
	Advanced stage disease	4.1 (1.3-12.9)
DFS	B symptoms	3.3 (1.3-8.7)
Overall survival	Age >45 yrs	2.1 (1-4.2)
	Male gender	3 (1.2-7.4)
	Advanced stage	3.7 (1.6-8.7)

## DISCUSSION

The aim of this study was to evaluate the prognostic factors for Hodgkin's lymphoma in a series of 100 adult patients who presented to the Medical Oncology Department at NCI, Cairo in the period between 1999 to 2001. Their median age was 37 years with 63% of the patients less than 45 years. This is comparable to

Vassilakopoulos et al., who reported a median age of 34 years with 70% of his cases below the age of 45 years [8]. Male to female ratio in our series was 2.1 : 1. This is comparable to that reported by other European and Egyptian data [5,9]. B symptoms were present in 31% of our cases, a figure which is comparable to Josting et al., who reported a figure of 47% [10] however it is a lower figure than the 64% reported by Smolewski et al., [9]. According to Ann Arbor staging we reported 17%, 34%, 37% and 12 % for stages I, II, III and IV; respectively. The corresponding figures reported by Smolewski et al. on his series of 327 patients were 8.6%, 33.6%, 42.8% and 15% for the four stages; respectively [9]. Mediastinal involvement was reported in 28% of our cases with a similar figure of 27.8% reported by Smoleski et al. [9].

All our cases are classical Hodgkin's lymphoma, pathological subtypes showed 48%, 31%, 20% and 1% for MC, NS, LP and LD; respectively. Similar figures were reported by other Egyptian authors [5]. This is in contrast to Western series who reported NS as the most frequent subtype [9,10]. Evaluation of prognostic factors for advanced stage disease showed TLC  $>15 \times 10^9/L$  in 15%, HB level  $<10.5$  gm/dl in 15% and serum albumin  $<4$  gm/dl in 64.3% of the cases. The corresponding figures reported by Vassilakopoulos et al. in his series of 333 patients with advanced HL were 22% for TLC  $>15 \times 10^9/L$ , 21% for HB level  $<10.5$  gm/dl and 68% for albumin level  $<4$  gm/dl [8].

At 4 years, the DFS of the whole group was 61.3%, while it was 69.8% and 45.1% in the early and advanced diseases; respectively. The DFS of the patients treated by ABVD was 94% versus 54.7% and 54.5% for COPP and COPP/ABV hybrid; respectively ( $p=0.2$ ). The corresponding figures in the Milan group was 81% for ABVD versus 63% for COPP [1]. Duggan et al. reported that ABVD alone was as equally effective as MOPP/ABV hybrid but less toxic and all combinations were more effective than MOPP alone [11]. Comparing the DFS of the ABVD regimen to the other two regimens showed borderline significance that could attain a significant value with larger number of cases. These data supported the more recent recommendation of considering ABVD as the standard regimen against which all experimental combinations are tested [1].

At 4 years, the OS of the early disease was 70.7% versus 38.9% for the advanced disease. The OS of the early disease is comparable to other groups using the same regimen while the OS of the advanced disease is poor compared to other groups who reported 5 years OS of 66% for MOPP, 75% to 87% for MOPP/ABV and 73% to 87% for ABVD [12].

In univariate analysis the prognostic factors that influenced the response to first line chemotherapy for the whole group were the stage of disease early versus advanced and gender with better response in females. This was also reported by others [9,12]. Extranodal involvement showed a trend for unfavorable response to chemotherapy in the early disease ( $p=0.09$ ). The significance of the extranodal involvement was reported by the German Hodgkin Study Group (GHSg) in their prognostic factors list. For the advanced stage disease, the response to first line chemotherapy was significantly influenced by gender with better response in females and a trend for significant adverse effect of hypoalbuminaemia ( $p=0.06$ ) Both factors were listed in the IPS for advanced stage HL and were significant factors as recorded by Vassilakopoulos et al. [8].

The DFS of the early disease was adversely affected by age, presence of B symptoms and elevated ESR ( $p$  values = 0.05, 0.03 and 0.04; respectively). This was consistent with the results of Smolewski et al. [9]. The DFS of the advanced stage disease was only correlated to gender with better response in females. This is in contrast to what was reported by Vassilakopoulos et al. who stated that stage IV and hypoalbuminaemia to be related to DFS. Both Vassilakopoulos et al. study and ours couldn't confirm the significance of age, Anemia and leucocytosis as prognostic factors for the advanced stage disease [8].

Regarding the OS of the whole group, age  $> 45$  years, advanced stage disease, presence of B symptoms and male gender were significant factors in our study and that of Smolewski et al. [9]. In the early disease, no significant correlation was found between OS and any of the studied factors, in contrast to Smolewski et al. who reported age and B symptoms to be related to OS [9]. This may be due to difference in the pattern of relapse and salvage therapy affecting the OS of the early disease.

The OS of the advanced group was affected by age and gender only. Vassilakopoulos et al. reported age, stage IV and hypoalbuminaemia as significant factors for OS in the advanced group [8].

Using multivariate regression analysis, the independent factors that negatively influenced the response to chemotherapy were male gender and advanced stage of disease. Smolewski et al. in his series of 327 patients reported bulky disease, advanced stage and age >45 years as independent prognostic factors for response to chemotherapy [9]. The OS was adversely affected by age >45 years, male gender and advanced stage of disease as found to be independent prognostic factors in our patients. In the present study, the performance status (PS) was not analyzed as the majority of the cases had a PS of 1 and 2. Smolewski et al. reported age >45 years, B symptoms, stage III and IV, Karnofsky's scale <70 and multisite localization >3 sites as independent prognostic factors for DFS and OS [9]. In our analysis, the presence of B symptoms was confirmed by multivariate analysis to be the only independent factor that adversely affected DFS of the whole group. Similarly, Diehl et al. considered systemic symptoms to be one of the major determinants for assigning Hodgkin's lymphoma patients to risk or prognosis adapted therapy [1].

Therefore we can conclude that our confirmed prognostic factors are in consistent with some other authors but the outcome from different studies are still controversial [8,9,13-15]. The adequate response and DFS of the early disease group compared to that of the advanced disease supported the evolving role of risk adapted chemotherapy of HL. The results of this study in the advanced disease are inferior to that reported by more aggressive chemotherapy regimens and needs to be improved in this potentially curable disease.

## REFERENCES

- Diehl V, Stein H, Hummel M, Zollinger R, Connors J. Hodgkin's lymphoma biology and treatment strategies for primary, refractory and relapsed disease. *Haematology (Am Soc Haemat ed program)*. 2003, 225-247.
- Ibrahim AS, Aref N. The registry of the National Cancer Institute in Cairo. Twelve years experience (1970-1981). *J Egypt Nat Cancer Instit*. 1984, 1: 1-12.
- El Bolkainy MN, Gad E I-Mawla NS, Tawfik HN, Aboul-Enein M. Epidemiology of lymphoma and leukaemia in Egypt. *J Egypt Nat Cancer Instit*. 1984, 1 (2): 9-16.
- Mokhtar N. Lymphohaemopoietic system in malignancy. NCI Cancer pathology registry between 1985-1989. *J Egypt Nat Cancer Instit*. 1991.
- Mokhtar N, Khaled H. *Lymphoma*. NCI (publisher). Cairo. 2002, 185-204.
- Tawfik HN, Aboul Ela F. Malignant lymphoma pathological features of 2010 Egyptian cases. *J Egypt Cancer Instit*. 1982, 1: 1-11.
- Bodis S, Henry-Amar M, Bosq J, Burgers J, Mellink W, Dietrich P, et al. Late relapse in early stage Hodgkin's disease patients enrolled on European Organization for research and treatment of cancer protocols. *J Clin Oncol*. 1993, 11: 225-232.
- Vassilakopoulos TP, Angelopoulou MK, Siakantaris ML, Barbounis A, Dimopoulou MN, Kontopidou FN, et al. Validation of the international prognostic score in patients with advanced Hodgkin's lymphoma treated in a single hematology unit. *Haema*. 2001, 4: 230-235.
- Smolewski P, Robak T, Krykowski E, Morawiec M, Niewiadomska H, Pluzaanska A, et al. Prognostic factors in Hodgkin's disease: Multivariate analysis of 327 patients from a single institution. *Clinical cancer research*. 2000, 6: 1150-1160.
- Josting A, Rueffer U, Franklin J, Siebe M, Diehl V, Engert A. Prognostic factors and treatment outcome in primary progressive Hodgkin lymphoma: A report from the German Hodgkin lymphoma study group. *Blood*, 2000, 96: 1280-1286.
- Duggan D, Petroni G, Johnson J. A randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: Report of an intergroup Trial. *J Clin Oncol*. 2003, 21: 607-614.
- Connors J, Noordijk E, Horning S. Hodgkin's lymphoma: Basing the treatment on the evidence. *Haematology (Am Soc Haemat ed program)*. 2001, 178-193.
- Wagstaff J, Gregory W, Swindell R, Crowthes D, lister T. Prognostic factors for survival in stage IIIB and IV. Hodgkin's disease: A multivariate analysis comparing two specialist treatment centers. *Br J Cancer*. 1988, 58: 487-492.
- Norberg B, Dige U, Roos G, Johansson H, Lenner P. Hodgkin's disease in Northern Sweden 1971-1981. II. A retrospective analysis of prognostic factors. *Acta Oncol*. 1991, 30: 597-601.
- Ranson MR, Radford JA, Swindell R, Deakin DP, Wilkinson PM, Harris M, et al. An analysis of prognostic factors in stage III and IV Hodgkin's disease treated at a single centre with MVPP. *Ann Oncol*.