

Treatment of Forty Adult Patients with Hodgkin Disease; Baghdad Teaching Hospital Experience

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Abstract:

Background: Hodgkin disease was the first cancer in which the curative potential of combination chemotherapy was demonstrated. The affected patients are often young and there is a great potential for adding years of productive life by giving curative therapy even when the disease is advanced.

Objective: to describe the experience of the hematology unit, Baghdad Teaching Hospital, in the management of 40 adult patients with Hodgkin disease.

Patients and Methods: a retrospective cohort study of forty adult Iraqi patients with Hodgkin disease between 2005 and 2013 in the hematology unit. Patients were treated initially with 6-8 cycles of ABVD chemotherapy protocol (doxorubicine+ bleomycin+ vinblastin+ dacarbazine) , nine patients received additional involved field radiotherapy for residual masses or bulky disease. Overall survival and progression free survivals were estimated using Kaplan Meier survival plot.

Results: The mean age was 28.6±12.88 years with females forming 61.5% of patients, mean duration of follow up was 27.9± 20.6 months. Staging showed that 55% and 27.5% had stage II and III respectively. B symptoms were found in 72.5% patients , bulky disease in 42.5% patients. Complete Response+ Complete Response undetermined was seen in 85% of cases. First Relapse occurred in 14%, and death in 7.5% of the patients. The 8 year overall survival and progression free survival were 82% and 50% respectively while the mean overall survival and progression free survival times were 84.7 and 59.9 months respectively.

Conclusion: The results of the treatment of adult patients with Hodgkin disease in our unit is rather comparable to the results from other studies.

Key words: Hodgkin disease, ABVD, Survival.

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Introduction:

In the current WHO lymphoma classification, Hodgkin Disease (HD) is subdivided into a classical form and a nodular lymphocyte predominant form .Classical HD, which accounts for about 95% of cases, is further subdivided into nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte depleted HD. This sub classification is largely based on differences in the morphology of the tumor cells and the histological picture.(1)The regimen of Doxorubicin+Bleomycin+Vinblastin+Dacarbazine (ABVD) was introduced in the mid-1970 as treatment in advanced Hodgkin lymphoma and become the standard treatment of this disease after a trial which showed that ABVD was as effective and even more effective than Mechlorethamine+ vincristine+ procarbazine + prednisone(MOPP) with less side effects. (2,3)The treatment of HD is one of the success stories of hematologic oncology. Cure rates have risen steadily over the last 6 decades, following the introduction first of extended field irradiation, then of

combination chemotherapy. Overall survival figures are now around 80% at 10 years. (4) Treatment of early-stage Hodgkin's disease is usually tailored in line with prognostic factors that allows for reductions in the amount of chemotherapy and extent of radiotherapy required for a possible cure. Although there was a trend in favor of the combined modality arm, a single-centre series suggested that six cycles of ABVD was effective and safe. (5)Chemotherapy plus involved-field radiotherapy(IFR) is currently the standard treatment for early Hodgkin's disease with favorable prognostic features. (6)The ABVD combination(2) was shown to be superior to MOPP, both in the remission rate and in its side-effect profile (7)and is now widely used as a standard treatment, albeit not universal. A series of attempts have been made to improve the treatment results further, using multiple chemotherapy agents, dose-intense schedules, and even myeloablative doses with overall 5-year progression free survival of around 70% in patients with advanced HD. German Hodgkin Lymphoma Study Group (GHSg) had developed a front-line intensified regimen consisting of bleomycin,

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etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (escalated BEACOPP regimen) for advanced disease with initial studies showing the results to be superior to alternating COPP-ABVD. (8) Overall, treatment with BEACOPP, as compared with ABVD, resulted in better initial tumor control, but the long-term clinical outcome did not differ significantly between the two regimens. (9)The current paper describes the experience of the hematology unit of Baghdad Teaching Hospital regarding the management of 40 cases of adult patients with Hodgkin disease.

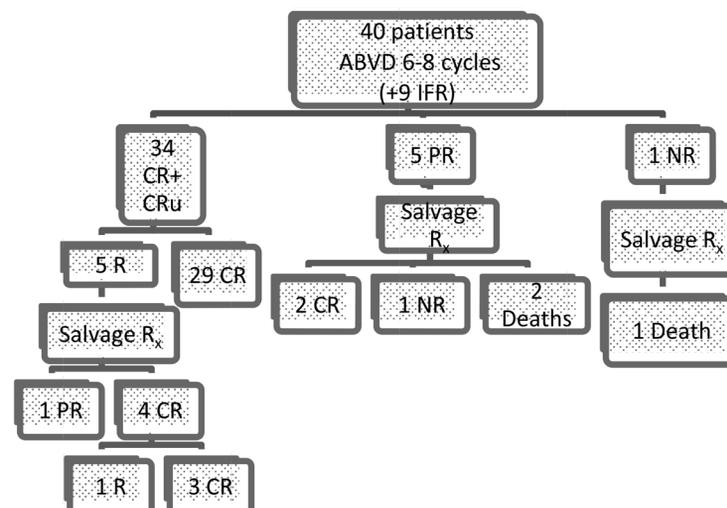
Patients and Methods:

This is a retrospective cohort study. During the period from April 2005 till March 2013, forty adult Iraqi patients with classical Hodgkin disease were diagnosed and managed in the hematology unit of Baghdad Teaching Hospital in Iraq. The patients were diagnosed by lymph node biopsy histopathological examination (confirmed by flow cytometry when available). Staging and evaluation were done by careful clinical evaluation along with blood counts, renal and liver function tests, serum albumin and lactate dehydrogenase (LDH) and spiral CT scan of neck, chest and abdomen with IV contrast and bone marrow aspirate and biopsy when indicated. The staging system was according to the Cotswold's modification of Ann Arbor staging system. (10) All patients gave their written consent for receiving the treatment. All cases included in this study were treated initially with 6-8 cycles of ABVD chemotherapy protocol (doxorubicin 25mg/m² iv, bleomycin 10mg/m² iv, vinblastin 6mg/m² iv and dacarbazine 375mg/m² iv day 1 and 15 every 28 days) according to the standard schedule. Nine patients received additional IFR for residual masses or bulky disease after the end of chemotherapy cycles. For patients who had partial response, non responders and those who relapsed after ABVD chemotherapy protocol, second and third line therapy with ICE (etoposide 100mg/m² for 3 days, Ifosfamide 5g/m² with mesna and carboplatin 450mg/AUC for day 1)

and GDP (Gemcitabine 1g/m² in day 1&8, cisplatin 75mg/m² day 1 and dexamethason 40mg iv infusion for 4 days) were administered, then re-assessment of the response was done. All patients had close follow up during treatment for managing treatment related toxicities. Definition of response criteria was done following the 4th and the last course of ABVD or other lines of treatment by clinical assessment and spiral CT scan of neck, chest and abdomen with IV contrast. PET CT scan was done for few patients who had a residual mass confirmed by CT scan. Assessment of response was according to the revised response criteria for Hodgkin lymphoma (excluding PET-CT). (11) Patients who attain remission were followed every 3 months for the first 2 years and then every 6 months for the next 3 years. The following information were collected for each patient; age, gender, histological type, Ann Arbor stage, Presence of mediastinal mass, bulky disease, ESR, WBC count, hemoglobin level, and serum LDH and albumin levels. Overall survival (OS) was estimated from date of diagnosis till state of being dead or alive at last follow up. Progression free survival (PFS) was estimated from day of diagnosis till progression from a complete or partial remission. Eight year rate of overall and progression free survivals and mean time of survivals were estimated using Kaplan Meier survival plots. Comparison of overall and progression free survivals according to stage was done using the Log rank test. A p value of < 0.05 was considered indicative of statistically significant difference. The statistical data were analyzed using Statistical Packages for Social Sciences (SPSS) version 18.

Results:

Between April 2005 and March 2013, 40 patients had been diagnosed and managed as Hodgkin disease in the hematology unit/Baghdad Teaching Hospital. Figure 1 showed the summary of the outcome of these patients with initial frontline treatment.



CR= Complete Remission, CRu= Complete Remission undetermined, PR=Partial Remission, NR= No Response, R= Relapse Figure 1: Outcome of 40 patients with Hodgkin's Disease

Thirty four patients achieved complete response (CR) + complete response undetermined (CRu) after completion of 6-8 courses of ABVD (+ 9 patients received IFR). Five patients had partial response (PR), 2 of them achieved CR after 2nd line treatment. One patient failed to respond to ABVD completely and had progression and died later on. Table 1 showed the characteristics of these patients, the age range was 14-62 years with a mean of 28.6 ± 12.88 years and 25 (61.5%) of them were females.

Table 1: Baseline characteristics of the patients

Characteristics	All Patients (40)	Missing Data
Age (in years) Range Mean \pm SD	14 - 62 28.62 \pm 12.881	None
Females.....No. (%)	25 (61.5)	None
Ann Arbor StageNo. (%)		
I	0 (0.0)	None
II	22 (55.0)	
III	11 (27.5)	
IV	7 (17.5)	
B symptomsNo. (%)	29 (72.5)	None
Histological Types.....No. (%)		
Lymphocyte rich classic	1 (2.5)	None
Nodular sclerosis	15 (37.5)	
Mixed cellularity	9 (22.5)	
Lymphocyte depletion	0 (0.0)	
Not classified	15 (37.5)	
Mediastinal MassNo. (%)	23 (57.5)	1
Raised S. LDHNo. (%)	9 (22.5)	7
Hb less than normal.....No. (%)	18 (45.0)	5
WBC \geq 15 X 10 ⁹ /L.....No. (%)	6 (15.0)	4
Bulky Disease.....No. (%)	17 (42.5)	1
Mean duration of follow up(in months)	27.9 \pm 20.6	
Median duration of follow up (in months)	21	

Around half of the patients had stage III and IV disease and more than half had a mediastinal mass. The mean and median duration of follow up were 27.9 ± 20.6 and 21 months respectively. Table 2 shows that initial CR+CRu was achieved in 34 patients (85%) after ABVD (+ 9 IFR) and subsequently 36 patients (90%) achieved CR+CRu after 2nd line treatment for 5 patients with partial response, with a rate of relapse of 14% from the 36 patients who had CR+CRu and 7.5% of the patients died during the period of study due to disease progression.

Table 2: Treatment outcome

Treatment outcome	Patients	
	No.	%
Initial Complete Remission (CR) + Complete Remission undetermined (CRu) after induction with ABVD (+ 9 IFR)	34	85
First Relapse (% from 36 patients with CR+ CRu)	5	14
Death	3	7.5

Table 3: Mean Survival time (in months)

Survival at 8 years	Mean	95% CI
Overall Survival	84.7	73 – 96.5
Progression Free Survival	59.9	44.6 – 75.1

Figure 2 and 3 showed that the 8 year overall survival and progression free survival were 82% and 50% respectively while the mean overall survival and progression free survival times were 84.7 and 59.9 months respectively.

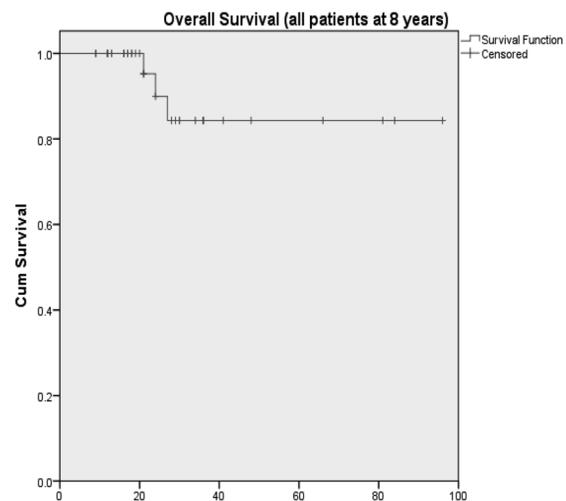


Figure 2: Duration of OS in months

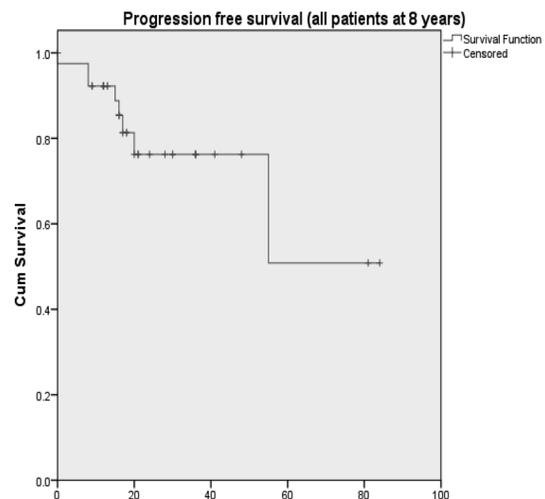


Figure 3: Progression free survival in months

Figure 4 and 5 showed the comparison of the progression free survival and overall survival of patient after stratification according to Ann Arbor disease stage using the Log Rank test and both showed a statistically significant difference in survival times according to stage (P values were 0.029 and 0.019 respectively).

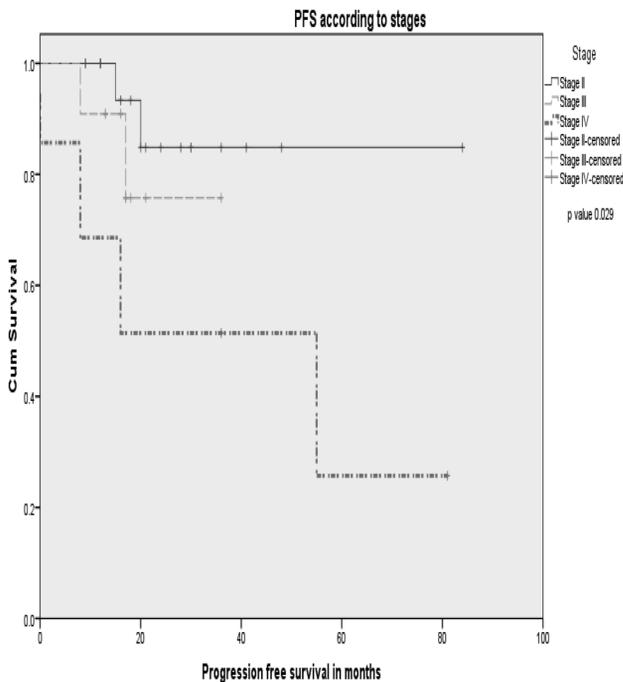


Figure 4 : Progression Free Survival according to disease stage

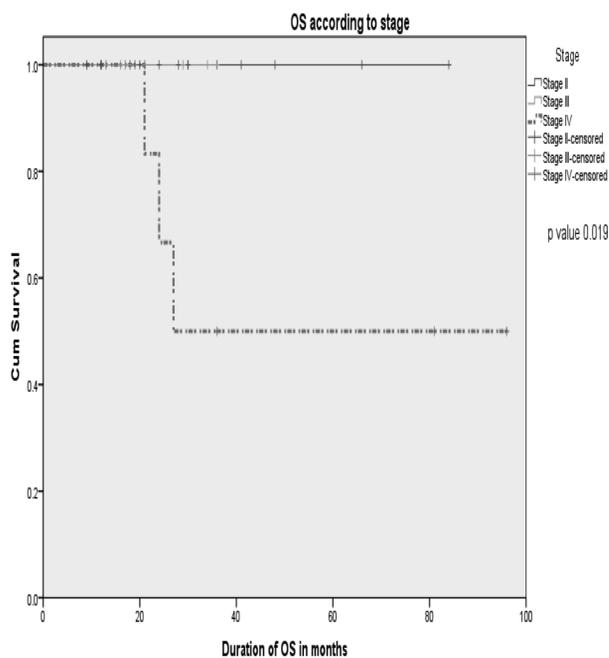


Figure 5 : Overall Survival according to disease stage

Discussion:

The current study aimed to describe the experience of the hematology unit of Baghdad Teaching Hospital in the treatment of forty Iraqi patients with Hodgkin disease. More than 50% of the patients were in stage II, but all were of the unfavorable group according to the EROTIC risk factors. The choice of ABVD as frontline therapy for all patients was consistent with different international guidelines and recommendations. (7,12) In this study, the rate of CR and CRu was 85% after frontline ABVD (+ 9 IFR) which became 90% after salvage therapy for patients not responding to the initial treatment, this rate is comparable to the results that had been published in 2009 from HD2000 Italian group, where the rates of CR and CRu was 84%, 91% for ABVD and BEACOPP respectively, all after chemotherapy and radiotherapy to the residual masses or slowly responding masses. These results are also comparable to the results of the German Hodgkin Study Group which published the 10 years follow up of HD9 trial, the CR rate was 85%, 88%, and 96% for COPP/ABVD, baseline BEACOPP, and escalated BEACOPP respectively. (13,14) The balance in the characteristics of the patients between our cohort and the above two studies is an important issue in trying to compare the results of our treatment and these trials, but a rapid review of the characteristics of our patients reveals many of them are of advance stage and they are a heterogeneous group. The second point that should be mentioned in this comparison, is the tools used in the assessment of remission, where in both these trials, even when the PET SCAN was used in the management, the final assessment of response depended on CT scan. So the CR and the CRu in the current study has the same level of evidence as in the previous studies. (13,14) Mitall R. et al. had published the single center experience in Kuwait, where 63 patients had been treated with combined modalities therapy with a remission rate of 87%. (15) One patient had progressive disease after ABVD, in addition three out of five patients who had partial remission failed to be salvaged by second line, so we have 10% early progression and three of them died due to disease progression (7.5%), the HD2000 trial reported the same percentage of progression and death in the ABVD arm, however the cause of death was due to disease progression in 50% of cases and treatment related in other 50% both first line and salvage therapy. The current study showed no report of any direct therapy related mortality. The profile of acute toxicity of ABVD (not mentioned in the result) also was comparable to the international numbers. (13,16) The fact is that this study has 10% of patients who cannot be salvaged by second line, and the cause of death was related to the disease activity, these figures seems comparable to the result of ABVD worldwide, this fact needs more and more analysis, especially when some studies pointed the superiority of more aggressive courses like escalated BEACOPP over ABVD. Here it can be concluded that more observation and pretreatment data may help to predict such nonresponders and to assign them for more aggressive approach as a first line. (13) The relapse rate in this study is comparable to that seen in the HD2000 Italian

group in the ABVD arm, which is 14%. The whole relapsed group was salvaged by second line therapy and the patients achieved a second CR. PET CT guided plans of therapy still cannot be implemented because we lack this facility. (13) The survival curves show comparable result with Italian, German, and the single center study from Kuwait, but we have seen a significant drop in the progression free survival, where it was 50% at 8 years. The 5 year PFS was 68% for the ABVD arm in the Italian study while the OS of the Kuwaiti study at 5.5 years was 91%. (13,14,15) a review of the Kaplan Meier PFS reveals that the drop in the curve was to the 78% at around 18 months and it remained in a plateau till a sudden drop near the end of the 5th year, where it drops to 50%, and this may indicate that some of the patients who are labeled as having CR were really not if they had been evaluated by PET CT scan. The significant difference in the OS and PFS between stage II and others was due to disease progression, disease related mortality, and relapse in the later, rather than therapy related toxicity. In conclusion the results of the treatment of adult patients with classical Hodgkin disease in hematology unit is rather comparable to the results from other studies in terms of rate of CR and OS but it seems inferior in regard of PFS. PET CT guided therapy and availability of autologous stem cell transplantation are needed to improve the treatment plan in the hematology unit.

Author contribution:

All authors contributed to patient registration, management and follow up.

Ali M. Jawad contributed in addition to that by gathering and analysis of the data and writing of the manuscript.

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