original research report

A randomized trial of brief treatment of early-stage Hodgkin lymphoma: Is it effective?

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Hematol Oncol Stem Cell Ther 2012; 5(1): 36-41

DOI: 10.5144/1658-3876.2012.36

BACKGROUND AND OBJECTIVES: Whether it is possible to reduce the intensity of treatment in early (stage I or II) Hodgkin lymphoma with a favorable prognosis remains unclear. Therefore, we conducted this randomized trial, comparing two treatment groups consisting of a combination chemotherapy regimen of two different intensities followed by involved-field radiation therapy at two different dose levels.

DESIGN AND SETTING: Prospective, randomized, in patients referred to the Department of Clinical Oncology and Nuclear Medicine.

PATIENTS AND METHODS: Ninety-eight patients with histologically proven early-stage Hodgkin lymphoma with a favorable prognosis were enrolled in this study between January 2008 and June 2010. They were randomly assigned in one of two treatment arms: arm I received four cycles of ABVD (Adriamycin, belomycin, vinblastine, dacarbazine) followed by 30 Gy of involved-field radiation therapy; arm II received two cycles of ABVD followed by 20 Gy of involved-field radiation therapy.

RESULTS: During the follow-up period, the 2-year relapse free survival rates were 96% and 95% in arm I and arm II, respectively(P=.8), while the 2-year overall survival rates were 98% and 95% in arm I and arm II, respectively (P=.16). Acute toxicity affected 54% of patients treated with four cycles of ABVD, who had grade III or IV toxicity, as compared with 30% of those receiving two cycles (P<.02). The rates of acute toxicity (grade III or IV) were also higher among patients treated with 30 Gy of involved-field radiation therapy than among those receiving 20 Gy (16% vs. 2.5%, P<.03) .

CONCLUSION: In patients with early-stage Hodgkin lymphoma and a favorable prognosis, treatment with two cycles of ABVD followed by 20 Gy of involved-field radiation therapy was as effective as, and less toxic than, four cycles of ABVD followed by 30 Gy of involved-field radiation therapy.

Hodgkin lymphoma (HL) is one of the most common malignancies in young adults and has become a curable malignancy for most patients in recent decades.[1,2] However, many controversies still exist on the optimal strategy of how to cure patients. The key question is how to balance the risks and toxicities of chemotherapy and radiotherapy against the need for a definite treatment for early or advanced-stage HL patients.[3]

The observation that patients suffering from early stage HL have a worse prognosis when certain clinical risk factors were present and thus need a more intensive therapy, lead to the definition of two prognostic groups: early favorable without clinical risk factors and early unfavorable with clinical risk factors. The definition of clinical risk factor is overlapping but not identical in major study groups. In the German Hodgkin Study Groups (GHSG) trials, the risk factors are large mediastinal mass, extranodal disease, involvement of 3 or more nodal areas and ESR ≥50 without B symptoms or ≥30 with B symptoms.[4,5]

For early-stage favorable HL, extended-field radiotherapy (EFRT) has been considered as standard treatment for more than two decades. However, EFRT has been abandoned by most study groups due to the recognition of late effects such as heart failure, pulmonary dysfunction, and secondary malignancies.[6,7] Instead, four cycles of ABVD followed by 30 Gy of involved-field radiation therapy are now regarded as the standard of care by many groups.[8] While consolidation radiotherapy is part of treatment for patients with early stage Hodgkin lymphoma in the European Society

of Medical Oncology (ESMO) clinical recommendations,[9] the National Comprehensive Cancer Network (NCCN) guidelines consider chemotherapy alone an alternative treatment option.[10]

Depending on intensity and dose of treatment, long-term complications such as secondary malignancis, cardiac disease and infertility are common in Hodgkin survivors.[9,11,12] In an attempt to reduce the toxic effects of treatment while retaining full control of the cancer, GHSG concluded from the results of a prospective, randomized, multicenter study (HD10) that patients with early- stage HL with a favorable prognosis, treatment with two cycles of ABVD (Adriamycin, belomycin, vinblastine, dacarbazine) followed by 20 Gy of involved-field radiation therapy is as effective as, and less toxic than, four cycles of ABVD followed by 30 Gy of involved-field radiation.[13]

The aim of this study was to determine whether fewer cycles of chemotherapy and lower doses of radiation therapy could be delivered to reduce the toxic effects of treatment, while maintaining high rates of disease control in patients with early Hodgkin lymphoma with a favorable prognosis who were undergoing combined-approach treatment programs.

PATIENTS AND METHODS

Between January 2008 and June 2010, 98 patients with newly diagnosed Hodgkin lymphoma in clinical stage I or II with a favorable prognosis who attended the Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospital, Mansoura, Egypt, were randomly assigned in this prospective study. Eligibility criteria included males and females older than 18 years, with an Eastern Cooperative Oncology Group (ECOG) performance status 0-1, histologically proven Hodgkin lymphoma in clinical stage I or II, with no clinical risk factors; B symptoms (fever ≥38°C, soaking night sweats, weight loss ≥10% within 6 months), extranodal disease, bulky disease (≥10 cm or >33% of the chest diameter on chest x-ray), three or more sites of nodal involvementand or a sedimentation rate of 50 or more, and no evidence of coexistent synchronous or previous malignant disease, previous radiotherapy, previous chemotherapy or previous surgery except biopsy only.

Pretreatment evaluation included a medical history, physical examination, complete blood work, electrocardiogram and neck, chest, abdominal and pelvic computed tomography (CT). Patients who fulfilled the above eligibility criteria were made aware of the purpose and the design of the study and required to sign the informed consent. Eligible patients were randomly assigned into two treatment arms. Arm I (n=50 patients) was treated by four cycles of ABVD followed by 30 Gy of involved-field radiation therapy. Arm II (n=48 patients) were treated by two cycles of ABVD followed by 20 Gy of involved-field radiation therapy.

ABVD was administered on days 1 and 15 in monthly cycles, at the following standard doses: doxorubicin, 25 mg per square meter of body surface area; bleomycin, 10 mg per square meter; vinblastine, 6 mg per square meter; and dacarbazine, 375 mg per square meter. If the white-cell count was less than 2500 per cubic millimeter or the platelet count was less than 80 000 per cubic millimeter on a day when chemotherapy was scheduled to be administered, treatment was postponed until normal levels were achieved. Granulocyte colony-stimulating factor was given if clinically indicated. During treatment, the patients were examined for acute toxicity every week. Toxicities were graded using the WHO Toxicity Criteria.[14]

Before treatment, all sites of disease were defined and documented. Patients were treated with external beam irradiation by a 6 MV linear accelerator planned as involved-field radiation according to the sites of disease. The recommended interval between completion of the ABVD regimen and the start of radiation therapy was 4 to 6 weeks. Patients received either 30 Gy or 20 Gy of involved-field radiation therapy in single fractions of 1.8 to 2.0 Gy administered five times weekly.

Response was assessed six weeks after completion of radiotherapy by clinical examination and neck, chest, abdominal and pelvic CT. Criteria for response were as follows: complete response (CR) was defined as complete regression of all evidence of tumor. Partial response (PR) was defined as an estimated decrease in tumor size of 50% or more. Stationary disease (SD) was defined as <50% decrease in tumor size or <25% increase in pretreatment tumor size. Progressive disease (PD) was defined as > 25% increase in pretreatment tumor size. Re-evaluation was done at 3 months interval during the first two years of follow-up. The primary efficacy end point was relapse-free survival. Overall survival and treatment toxicity were secondary end points

All data were categorical and represented as number and percent. The baseline characteristics and adverse effects of the two treatment arms were compared using the Chi-square test. Confidence intervals (CIs) were calculated using the Cox proportional hazard model. Overall survival and relapse free survival for the two groups were calculated using the Kaplan-Meier method. Informed consent was obtained from all patients, and ethical committee approval was received by our participating center. The randomization scheme was a

permuted block design with an equal probability of assignment to either treatment arms. Patients were stratified by primary site of disease and stage of disease and were then randomized to receive one of the two treatments planned in the trial.

RESULTS

From January 2008 to June 2010, 98 patients were recruited and randomly assigned into two treatment arms, either arm 1 with 50 patients or arm II with 48 patients. In arm II, 8 patients were excluded from all analyses: 2 becuase of incorrect initial staging, 2 who could not subsequently be contacted and 4 who refused the reduced treatment regimen after randomization. A total of 90 patients received complete treatment as defined per protocal or with an acceptable variation.

The baseline characteristics of the study patients are shown in **Table 1**. No significant differences were noted between treatment arms for any of the characteristics. The median age of patients at randomization was 26 years (range, 18 to 44), and 66.7% were male. Infradiaphragmatic disease was present in 11.1%. The most frequent subtype diagnosed by the pathology reference panel was nodular sclerosing (46.7%). Ann Arbor staging was 55.6% for stage IA disease, 11.1% for stage IB, 28.9% for stage IIA, and 4.4% for stage IIB. Response assessment was done 4-6 weeks after the completion of treatment. All patients achieved a clinical complete response (CR) or CR unconfirmed in both arms.

Acute toxicity during chemotherapy was more frequent in patients who received four cycles of ABVD than in those who received two cycles (**Table 2**). Overall, 54% of the patients who received four cycles of ABVD had at least one instance of severe toxicity (grade III or IV) as compared with 30% of those who received two cycles (P=.02). The most frequent events were hair loss (in 28% of patients receiving four cycles vs. 15% of those receiving two cycles) and hematologic toxic effects (28% vs. 10%). Infections and pulmonary fibrosis were also more common with four cycles of ABVD than with two cycles (4% vs. 0%)for each of

Table 1. Characteristics of 90 patients with early stage Hodgkin lymphoma by treatment arm.

Character	Total		Arm I		Arm II		*P*
	No.	%	No.	%	No.	%	
Age (years)							
<30	78	86.7	40	80	38	95	.0590
≥30	12	13.3	10	20	2	5	
Sex							
Male	60	66.7	32	64	28	70	.6542
Female	30	33.3	18	36	12	30	
Site							
Supradiaphragmatic	80	88.9	42	84	38	95	.1754
Infradiaphragmatic	10	11.1	8	16	2	5	
Histologic type							
Mixed cellularity	28	31.1	16	24	12	30	.8353
Nodular sclerosing	42	46.7	22	44	20	50	
Lymphocyte-rich	20	22.2	12	32	8	20	
Lymphocyte-depleted	0	0	0	0	0	0	
Ann Arbor stage							
I A	50	55.6	24	48	26	65	.6889
I B	10	11.1	6	12	4	10	
II A	26	28.9	16	32	10	25	
IIB	4	4.4	2	4	2	5	

them. Severe toxicity (grade III or IV) was observed more often among the patients treated with 30 Gy of involved-field radiation therapy than among those who received 20 Gy (16% vs. 2.5%, *P*=.03). The most common sites of grade 3 or worse acute side effects were the skin , the mucous membranes and the pharynx. Acute toxicity was higher in arm I but was tolerable and manageable.

The relapse rate was 4.4 % (4 of 90). No significant differences were seen in rates of relapse in either arm. The rates of relapse-free survival in the whole analysis set of 90 patients were estimated to be 95.6% (95% CI: 89.1 to 98.2) at 2 years.

The overall survival rates for all 90 patients were estimated to be 96.7 % (95% CI: 90.7 to 98.8) at 2 years. The median observation time for the primary end point, relapse-free survival, was identical in the two chemotherapy arms (28 months). Relapse free survival at 2 years was 96% in arm I (95% CI: 86.5 to 98.8) and 95% with arm II, (95% CI: 83.4 to 98.5) with no statistically significant difference (*P*=.8) . Results of Kaplan-Meier estimates of relapse free survival in both treatment arms are shown in **Figure 1**. At a median follow-up of 30 months of all analyzed patients, the median overall survival in armI was 28 months, ranging from 14 to 39 months vs 27 months, ranging from 12 to 39 months in arm II, with no statistically significant difference (*P*=.16) The 2-year overall survival in arm I was 98% (95% CI: 88.5 to 99.8) vs 95% (95% CI: 83.4 to 98.5) in arm II, with no statistically significant difference (*P*=.43) (**Figure 2**).

A total of 3 patients died during the follow-up period. The causes of death were toxicity of primary therapy in one patient treated with four cycles of ABVD (died from pneumonia), toxicity of salvage therapy in one patient assigned to two cycles of ABVD (died from sepsis) and not specified in one patient assigned to arm II.

DISCUSSION

One of the key objectives in the treatment of Hodgkin lymphoma is to reduce the intensity of first-line therapy as much as possible while maintaining tumor control. This is most relevant for early disease with a favorable prognosis, which accounts for about 30% of all cases of Hodgkin lymphoma.[15] In our study, the results showed noninferiority for both fewer cycles of chemotherapy and a lower dose of radiation, in comparison with more intensive treatment . No difference in efficacy was noted between both arms. This was true for the primary end point of relapse-free survival at 2 years that was 96% in arm I (95% CI: 86.5 to 98.8) and 95% in arm II, (95% CI:83.4 to 98.5) with no statistically significant difference (*P*=.8). For all other efficacy end points, such as response there was no statistically significant difference. Similar results were confirmed by a large clinical trial by the German Hodgkin Study Group (GHSG). GHSG HD[10] compared four cycles with two cycles of ABVD; both followed either 30 or 20 Gy RT, respectively. Importantly, the weakest combination was not inferior to any other combination. Thus, two cycles of ABVD, followed by 20 Gy IFRT, are the new treatment standard for early favorable HL patients.[11,13] In our study, the relapse rate was only 4% (4 of 90). in the

Table 2. Acute adverse effects (grade III or IV) in both treatment arms.

Event	Arm I		Arm II	
	No.	%	No.	%
Anemia	2	4	0	0
Thrombopenia	2	4	0	0
Leukopenia	12	24	4	10
Nausea or vomiting	6	12	4	10
Pulmonary fibrosis	2	4	0	0
Hair loss	14	28	6	15
Infection	2	4	0	0
Skin toxicity (dermatitis)	2	4	0	0
Mucous membrane (mucositis)	4	8	1	2.5
Pharynx /Esophagus (dysphagia)	2	4	0	0

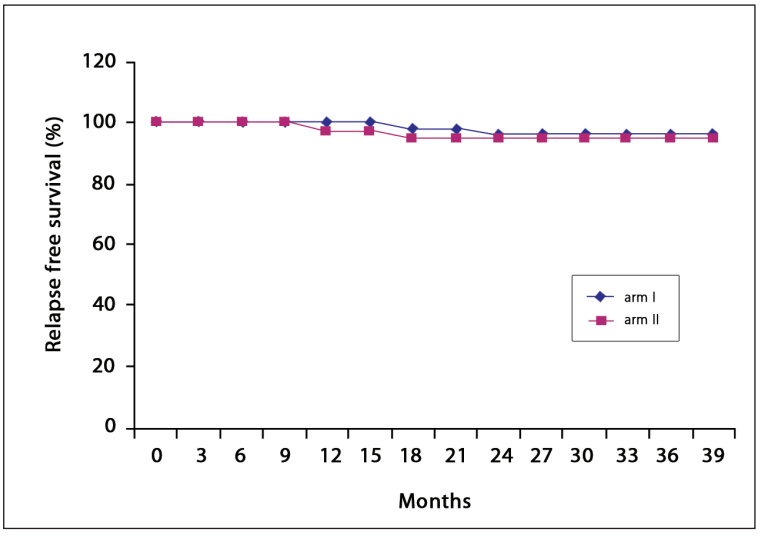

Figure 1. Relapse-free survival in the two treatment arms.

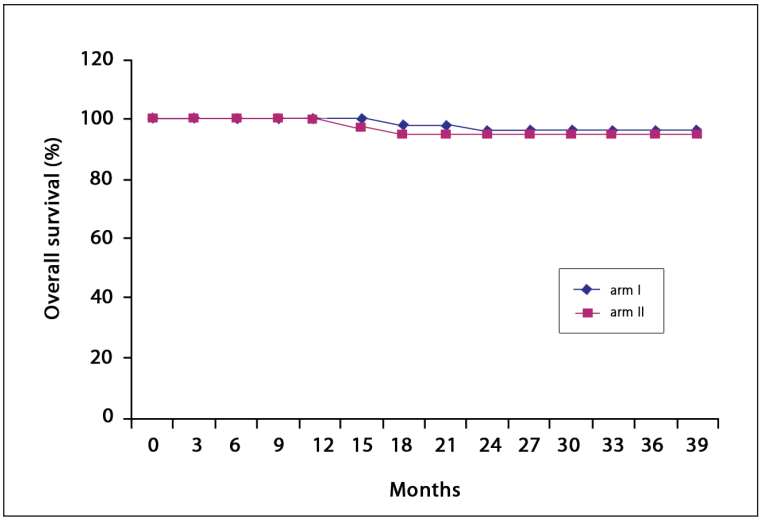

Figure 2. Overall survival in the two treatment arms.

same context Sieniawski et al[8] reported the same percentage among 1129 patients with early-stage favorable Hodgkin lymphoma enrolled onto the HD7/HD10/HD13 trials of the German Hodgkin Study Group. Forty-two patients (3.6 %) had treatment failure.

In terms of treatment complications, in our study, two cycles of ABVD as well as 20 Gy of radiation resulted in reduced rates of acute toxicity. Overall, 54% of patients treated with four cycles of ABVD had grade III or IV toxicity, as compared with 30% of those who received two cycles ($P<.02$). The rates of acute toxicity (grade III or IV) were also higher among patients treated with 30 Gy of involved-field radiation therapy than among those received 20 Gy (16% vs. 2.5%, $P<.03$). in the same context Connors,[16] Yahalom[17] and Nachman[18] reported that a shorter chemotherapy regimen with a lower radiation dose preserves a high level of disease control with lower toxicity.

Clearly, longer follow-up is needed to identify long-term toxicity, such as secondary neoplasm and severe organ damage. Given that many of the late, fatal complications of radiation therapy do not emerge until the second decade after treatment, our study cannot speak to the effect of treatment on overall survival. As the follow-up is short differences may appear with a longer duration of follow-up, so these results are considered preliminary and reanalysis is planned after another 3 years.

Currently, risk factors do not allow identification of patients who can be cured with even less treatment. The use of positron-emission tomography (PET) might help to discriminate between patients at low risk and those at high risk. Several ongoing trials are evaluating the role of PET in identifying patients with early Hodgkin lymphoma and a favorable prognosis who might not need additional radiation therapy after a brief chemotherapy course.[19-21]

Author contributions

RHH contributed the idea, treatment protocol, and writing of the paper. AHA contributed the treatment protocol, writing of the paper, and IAA reviewed the manuscript. No conflicts of interest were declared.

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