Original Study

Chemoresistance As a Function of the Pretherapy Tumor Burden and the Chemotherapy Regimen Administered: Differences Observed With 2 Current Chemotherapy Regimens for Advanced Hodgkin Lymphoma

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Abstract

Chemoresistance can be disclosed by incomplete response or early relapse. The tumor burden of Hodgkin lymphoma was assessed in 115 patients treated with ABVD and 107 with BEACOPP and demonstrated to be the best predictor of resistance. For the same tumor burden ABVD has higher risk of resistance than BEACOPP and it should be considered in the choice of treatments.

Background: The mature results from trials comparing ABVD (Adriamycin [doxorubicin], bleomycin, vinblastine, dacarbazine) and BEACOPP (bleomycin, etoposide, Adriamycin [doxorubicin], cyclophosphamide, Oncovin [vincristine], procarbazine, prednisone) chemotherapies in advanced Hodgkin lymphoma will be available in some years. An early comparison of their curative potential can however be obtained from an assessment of initial tumor burden and chemoresistance. **Patients and Methods:** Less than a complete remission after treatment and relapse occurring within 12 months thereafter were assumed to be clinical expressions of chemoresistance. The tumor burden was calculated from the measurements of all the lesions documented by staging computed tomography (CT) and was normalized to body surface area to give the relative tumor burden (rTB). Using logistic regression analysis, the relationship between initial rTB, chemoresistance, and chemotherapy regimen administered was retrospectively studied in 222 patients selected from those enrolled in 2 similar randomized trials. **Results:** The median rTB volumes were 157.9 cm^3/m^2 in the 115 patients treated with ABVD vs. 154.6 cm^3/m^2 in the 107 patients treated with BEACOPP, and the distribution of the volumes was identical in the 2 groups. The rTB was confirmed as the best predictor of early treatment failures (22 less than complete responses plus 21 early relapses). For the same rTB, the risk of chemoresistance to BEACOPP was about half that of the chemoresistance to ABVD or, for a given risk of chemoresistance, BEACOPP cured patients with an rTB 89.1 cm^3/m^2 greater than that cured by ABVD (ie, more than 50% of the median tumor load of patients with advanced-stage disease). **Conclusion:** This account of rTB allows an early comparative evaluation of the curative ability of different chemotherapy regimens.

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Introduction

Several large randomized trials have indicated that the activity of ABVD (Adriamycin [doxorubicin], bleomycin, vinblastine, dacarbazine) in patients with advanced Hodgkin lymphoma is equivalent or even superior to that of MOPP (mechlorethamine, Oncovin [vincristine], procarbazine, prednisone) as well as to that of any other hybrid or alternating schedule that combines the drugs of both regimens.[1-4] Many efforts have been made to further improve the efficacy of ABVD, and several new regimens were designed and tested to this aim, such as Stanford V, MOPPEBVCAD (mechlorethamine, Oncovin [vincristine], procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, CCNU [lomustine], doxorubicin, desacetyl vinblastine amide sulfate [vindesine]), ChlVPP/PABlOE (chlorambucil, vinblastine, procarbazine, prednisone/prednisone, Adriamycin [doxorubicin], bleomycin, Oncovin [vincristine], etoposide), ChlVPP/EVA (chlorambucil, vinblastine, procarbazine, prednisone /etoposide, vincristine, and Adriamycin [doxorubicin]), and VEBEP (Vepesid [etoposide], epirubicin, bleomycin, Endoxan [cyclophosphamide], prednisone).[5-8] So far none of these has been shown to be more effective than ABVD, thus making ABVD chemotherapy the standard of treatment for patients with advanced Hodgkin lymphoma. Recently however the excellent results obtained with an intensified combination therapy including bleomycin, etoposide, Adriamycin (doxorubicin), cyclophosphamide, Oncovin (vincristine), procarbazine, and prednisone (BEACOPP)[9,10] raised hopes that this regimen may be superior to ABVD. The early results of the first 2 very similar randomized trials[11,12] directly comparing ABVD and BEACOPP suggest that these hopes are probably being met, at least in certain presentations.

In order to identify the more effective of these 2 regimens and to contribute additional information on the risk-benefit ratio of a given chemotherapy in any patient treated, we retrospectively investigated the relationship between pretherapy tumor burden and both response and durability of the response. For this purpose we used the large number of patients who entered the 2 recent trials comparing ABVD and BEACOPP. Since the achievement of less than a complete remission after therapy and the occurrence of early relapse both reflect in essence a degree of chemoresistance, this study can be considered an attempt to determine the relationship between initial tumor mass and development of chemoresistance distinctly for each chemotherapy regimen administered. Chemoresistance was preferred to other endpoints, such as estimated failure-free or progression-free survival, because it represents an early and directly recorded parameter, sufficiently related to the types and dosages of the drugs administered, and with a lower probability of interference by other factors (eg, late toxicity, intercurrent diseases, deaths from other causes).

Materials and Methods

Patients

The study population consisted of a considerable portion of the patients enrolled in the 2 recent trials comparing ABVD and BEACOPP: the trial by the GISL (Gruppo Italiano per lo Studio dei Linfomi)[11] and that by the FM-GITIL-IIL (Fondazione Michelangelo—Gruppo Italiano Terapie Innovative nei Linfomi—Intergruppo Italiano Linfomi).[12] The inclusion criteria (with stratification by stage [IIB, III, IV]) and the exclusion criteria for these studies were identical; they both enrolled cases during the same period (from 2000 to 2007) and adopted the same International Working Group response criteria defined by Cheson et al.[13] Baseline clinical characteristics of the patients randomized in both studies were similar, except there was a higher number of patients with bulky disease and with an International Prognostic Index (IPI) score[14] ≥ 3 in the FM-GITIL-ILL trial (57% vs. 34% and 54% vs. 36%, respectively). These differences however are not present in the treatment groups pooled and compared in this study (Table 1). In both trials patients were randomized to receive either ABVD or BEACOPP and were allowed limited radiotherapy either to sites of initial bulky disease or

Table 1 Staging Characteristics, Treatment Modalities, and Response of the Patients Treated With Either ABVD or BEACOPP Chemotherapy

Variable	ABVD (115)		BEACOPP (107)	
	No.	%	No.	%
Male sex	61	53	68	64
Age > 45 years	21	18	16	15
Stage II Disease	47	41	31	30
Stage III Disease	48	42	38	35
Stage IV Disease[a]	20	17	38	35
B Symptoms	80	70	80	75
Lymphocyte Predominance	5	4	4	4
Nodular Sclerosis	76	66	71	66
Mixed Cellularity	24	21	24	22
Lymphocyte Depletion	9	8	7	6
Unclassifiable Histologic Type	1	1	1	1
Bulky Mass	43	37	42	39
Marrow Involvement	8	7	10	9
ESR > 45 mm 1st hour	78	68	69	66
Hemoglobin value < 10.5 g/dL	22	19	23	21
Serum Albumin level < 4.0 g/dL	68	59	57	54
LDH level > 450 U/L	30	26	36	33
WBC count > 16 × $10^3/\mu L$	16	14	15	14
Lymphocytes < 0.6 × $10^3/\mu L$	12	10	7	7
IPI score > 3	46	40	49	46
Radiotherapy	64	56	47	44
Complete Remission	102	88	98	91
Partial Remission	3	3	2	2
Null Response	3	3	3	3
Progression	7	6	4	4
Early Relapse	15	13	6	6
Mean Chemotherapy Dose Intensity	0.90 ± 0.12		0.81 ± 0.11	

Abbreviations: ESR = erythrocyte sedimentation rate; IPI = International Prognostic Index on Advanced Hodgkin's Disease; LDH = lactate dehydrogenase; WBC = white blood cell.
[a] Difference among groups is statistically significant ($P = .04$), but does not influence the results (see Discussion section).