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ORIGINAL ARTICLE

Low incidence of long-term respiratory impairment in Hodgkin lymphoma survivors

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Abstract Introduction of new chemotherapy regimens over the last decade resulted in 90% survival in patients with Hodgkin lymphoma (HL), which enhances significance of abrogating chemotherapy-related long-term toxicities in young subjects. The present trial evaluated incidence of long-term respiratory complications associated with adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) or bleomycin sulfate, etoposide phosphate, doxorubicin hydrochloride (Adriamycin), cyclophosphamide, vincristine sulfate (Oncovin), procarbazine hydrochloride, and prednisone (BEACOPP). Sixty-seven HL patients, 21 treated with ABVD and 46 with BEACOPP, underwent prospective respiratory evaluation. Median follow-up from chemotherapy completion to respiratory assessment was 61 months. Abnormal lung function tests (LFT) were found in nine patients (13.6%)—three with functional dyspnea and six asymptomatic—with reduced DLCO (≤70%), VC, and TLC. Previous history of bleomycin pulmonary toxicity was found to be the only statistically significant factor for chronic respiratory impairment (75% vs. 10%, p=0.007, relative risk (RR)=28; 95% CI, 2.5–313). However, abnormal LFT tended to occur more frequently in patients receiving mantle field irradiation (18% vs. 9%, RR=2.2), those who experienced respiratory infection (25% vs. 13%, RR=2.25), and patients treated with ABVD compared to BEACOPP (19% vs. 11%, RR=1.9). Long-term respiratory impairment in HL survivors is unusual and rarely results in functional discomfort. BEACOPP is "respiratory safe," being associated with a nonsignificant risk for long-term respiratory dysfunction.

Keywords Hodgkin lymphoma · Respiratory toxicity · Bleomycin · BEACOPP

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Introduction

The management of Hodgkin lymphoma (HL), the second most common cancer in young subjects aged 15–60 [1], has become one of the true success stories in malignant hematology. Application of new chemotherapy regimens, such as bleomycin sulfate, etoposide phosphate, doxorubicin hydrochloride (Adriamycin), cyclophosphamide, vincristine sulfate (Oncovin), procarbazine hydrochloride, and prednisone (BEACOPP) or escalated BEACOPP, over the last decade, resulted in a 10-year freedom from treatment failure and overall survival (OS) of 82% and 86%, respectively, including patients presenting with a poor risk disease [2]. These encouraging survival rates emphasize the importance of preventing chemotherapy-related long-term toxicities in these young subjects [3, 4]. One of the major concerns in HL is chronic treatment-related respiratory impairment, associated with bleomycin [5–8] and mediastinal irradiation. The present study investigated long-term respiratory complications of the most recent chemoradiotherapy for HL, focusing on patients currently treated with either adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) or the novel regimen, BEACOPP, aiming to define

the potential "price" of these very efficient emerging therapies.

Patients and methods

The study was approved by the IRB of the Rambam Medical Center (approval number 3035). The departmental lymphoma database was searched for all patients diagnosed with HL between 1999 and 2005, who received a first-line therapy and remained in complete remission. Patients meeting these criteria were invited to sign an informed consent and participate in the trial. The study period was chosen to ensure a sufficient follow-up of at least 3 years since therapy completion that would enable a reliable assessment of long-term treatment-related respiratory complications. Patients participating in the study were prospectively assessed in terms of their respiratory status.

Data collection

The majority of patients diagnosed with HL between 1995 and 2005 participated in the previously reported phase II clinical trial (National Clinical Trial (NCT) 305149) [9]. Therefore, data on most of the patients (n=51, 76%), apart from findings related to their current pulmonary function, were retrieved from the Case Report Forms (CRFs), filled in prospectively at the time of diagnosis and treatment in the setting of the NCT 305149 study. For the individuals who had not taken part in the prior trial, relevant data were retrospectively collected from original medical files. The review of patient information focused on the following parameters: previous history of lung disease (prior to HL diagnosis), smoking, HL lung involvement, preexisting renal impairment, HL treatment protocol, cumulative dose of bleomycin (measured in milligrams per square meter), administration of mediastinal radiotherapy, including radiotherapy dose, as well as infectious and noninfectious respiratory complications reported during treatment.

HL treatment protocol

All participants were treated with bleomycin-containing regimens, which were chosen according to the patient risk factors at diagnosis. Standard-risk patients received ABVD (doxorubicin 25 mg/m^2, bleomycin 10 mg/m^2,vinblastine 6 g/m^2, and dacarbazine 375 mg/m^2) given with dexamethasone 20 mg every 14 days. Patients treated with tailored BEACOPP received either standard BEACOPP (SB) or escalated BEACOPP (EB) (bleomycin 10 mg/m^2, vincristine 1.4 mg/m^2, procarbazine 700 mg/m^2, and prednisone 280 mg/m^2 for both SB and EB; etoposide 300 mg/m^2 in SB and 600 mg/m^2 in EB; doxorubicin 25 mg/m^2 in SB and 35 mg/m^2 for EB, cyclophosphamide 650 mg/m^2 for SB or 1,250 mg/m^2 in EB). Therapy was tailored according to pretreatment risk assessment and changed according to interim scintigraphy as previously reported [9]. High-risk subjects presenting with an international prognostic score (IPS) of ≥3 [10] were initially treated with two cycles of EB, and patients with IPS 0–2 received two cycles of SB. Following interim scintigraphy, additional four cycles of SB were given to patients with a negative result, and only those with a positive study received four cycles of EB. A total of six cycles of BEACOPP were given. Adjuvant mediastinal radiotherapy was administered to patients presenting with a bulky mediastinal disease (≥10 cm).

Pulmonary assessment

Enrolled patients were examined by a single pulmonary physician and underwent a detailed respiratory evaluation, including pulmonary function tests. Patient medical history was analyzed, with a special emphasis on current respiratory symptoms, including cough, recurrent pulmonary infection, and dyspnea. Dyspnea intensity was rated using the modified Borg scale [11] and the Medical Research Council (MRC) Dyspnea scale [12, 13].

Lung function tests included oxygen saturation, measured at rest, during and after completing 5 min of exercise, diffusing capacity of carbon monoxide (DLCO), vital capacity (VC), total lung capacity (TLC), forced volume vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and FEV1/FVC. Pulmonary function was evaluated according to the American Thoracic Society standards, using a single piece of equipment: ZAN, Messgeräte GmbH, Germany. The system was calibrated daily according to the guidelines [14–18]. DLCO was measured by a standard single-breath method and corrected for the hemoglobin level. All pulmonary function values, except for the FEV1/FVC ratio, were presented as percentages of the predicted values. Predicted values were adjusted for sex, age, height, and weight. FVC, FEV1, TLC, FEV1/FVC, and DLCO were classified into two categories: above versus equal or below 70%. The diffusion coefficient was estimated as the DLCO/alveolar volume ratio.

Statistical analysis

Statistical analysis was performed using SPSS version 17. Descriptive statistics included means, standard deviations, and frequencies. Independent sample t tests were used to analyze differences between central variables by treatment type groups and toxicity groups. Correlation analysis was done by using the Pearson rank correlation test. A correlation coefficient was considered to be positive if

higher than 0.1. Univariate regression analysis was performed.

Results

One hundred and seventy-six HL patients were treated at the Rambam Medical Center during the study period. Eleven patients died: seven due to disease progression or relapse and four due to lymphoma-unrelated causes, while being in complete remission (one cardiac event, one carcinoma of the breast, one acute myeloid leukemia, and one suicide). One hundred and sixty-five patients were found to be potential candidates for the study. Fourteen patients were contact failures, 82 individuals were not interested in participating in the study, and 67 agreed and completed the study.

Patient characteristics of the whole study group as well as in correlation with the treatment protocol are presented in Table 1. The median age at diagnosis was 30 years (19–79). A medical history of smoking, previously existing lung disease, and HL-related lung involvement was recorded in 23 (34%), 5 (7.5%; 3 childhood asthma, 1 unexplained recurrent episodes of pneumonia, and 1 radiological findings compatible with "old tuberculosis"), and 2 (3%) patients, respectively. None of the patients presented with a preexisting kidney impairment. Forty-six patients received six cycles of tailored BEACOPP (24 patients, six cycles of SB; 4 patients, six cycles of EB; 12 patients, two cycles of EB+four cycles of SB; 6 patients, two cycles of SB+four cycles of EB). Twenty-one were treated with the ABVD regimen. Three patients, treated with two courses of EB followed by four courses of ABVD, were analyzed in the ABVD group. It is noteworthy that patients included in this

Table 1 Patient characteristics

	Total (67)	ABVD (21)	BEACOPP (46)	P value
Gender (male/female)	40/27	12/9	28/18	NS
Age (years, mean ,±SD)	13±,38	38±15	38±11.5	NS
Smoking	23(34%)	7(33%)	16(35%)	NS
Previous lung disease	5(7%)	0	5(11%)	0.02
Stage of HL) freq)				
I	1(1.5%)	0	1(2.2%)	NS
II	39(58%)	15(71.5%)	24(52%)	NS
III	7(10.5%)	3(14%)	4(9%)	NS
IV	17(25%)	1(5%)	16(38%)	0.01
Unknown	3(4.5%)	2(9.5%)	1(2%)	NS
HL-Lung involvement	2(3%)	1(5%)	1(2%)	NS
Bleomycin dose(mg/m^2)				
60	46(69%)	0	46(100%)	0.000
80	7	7(33.3%)	0	0.000
100	2	2(9.5%)	0	0.000
120	12	12(57%)	0	0.000
Mantle cell radiotherapy	34(51%)	12(57%)	22(48%)	NS
Radiotherapy dose (cGy)	2895±50	2682±22	2992±57	0.03
Respiratory symptoms during therapy				
BPT	4	3(14%)	1(2%)	0.000
Infections	4	0	4(9%)	0.000
Unspecified	4	2(9.5%)	2(4%)	0.000
Abnormal lung function test				
Total	97	4(19%)	5(11%)	NS
VC(%)		1 (5%)	6 (13%)	0.01
TLC(%)	6	2 (9.5%)	4(8.6%)	NS
DLCO(%)	9	4(19%)	5(11%)	NS
Time from treatment cessation to respiratory assessment (months)	61±26	49±22	66±27	0.01

BPT bleomycin pulmonary toxicity (acute and sub-acute)

study were treated according to their risk group, irrespective of a previous history of lung disease.

Thirty-four patients (51%) received adjuvant radiotherapy involving the mediastinum (median dose, 2,895.62 cGY; ranging between 2,500 and 4,320). Acute and subacute treatment-related respiratory complications were reported in 12 patients (18%: 4 developed lung infection, 4 experienced a bleomycin-related pulmonary toxicity (BPT), and 4 were categorized as having nonspecific respiratory symptoms).

The median follow-up from completion of chemotherapy to respiratory assessment was 57 months. Abnormal lung function tests were detected in 14 patients (20.8%). Five patients were excluded from further analysis due to a non-parenchymal dysfunction: two diaphragmatic paralysis, one morbid obesity, one musculoskeletal disease, and one post-pleurodesis. Parenchyma-related abnormal lung function tests were recorded in nine patients (13%).The characteristics of these nine patients, six asymptomatic and three symptomatic (functional dyspnea, MRC 1; Borg dyspnea 2), are presented in Table 2. Median age at diagnosis of the "respiratory-impaired cohort" was 34 years, ranging from 26 to 52 years. Five patients were treated with tailored BEACOPP: three patients received six cycles of SB; one patient, two cycles of EB+four cycles of SB; and one patient, two cycles of EB+ four cycles of SB. Four individuals were treated with the ABVD regimen. The cumulated dose of bleomycin for all patients, except for one, approached 60 mg/m^2. Six patients, three in the BEACOPP cohort and three in the ABVD cohort, also received adjuvant mediastinal radiotherapy postchemotherapy, with a median dose of 2,876 cGy (range, 2,500–4,320 cGy). None of the patients suffered from lung disease prior to the HL diagnosis. However, three patients experienced bleomycin pulmonary toxicity (BPT)—two treated with ABVD and one treated with BEACOPP. BPT was successfully managed with discontinuation of bleomycin and administration of steroids.

Risk factors for treatment-related respiratory impairment

A univariate analysis, including patient characteristics, disease- and treatment-related parameters (Table 3), identified a previous history of BPT to be the only statistically significant factor for long-term therapy-related respiratory impairment (75% vs. 10%, respiratory rate (RR)=28; 95% confidence interval (CI), 2.5–313). However, the incidence of abnormal lung function tests tended to be higher in patients receiving mantle field irradiation (18% vs. 9%, RR= 2.22, CI 0.5–9.7), those who experienced treatment-related respiratory infections (25% vs. 13%, RR=2.25,CI 0.2–24), patients treated with ABVD compared to BEACOPP (19% vs. 11%, RR=1.9,CI 0.45–7.8), and males vs. females (11.5% vs. 15%, RR=1.35,CI 0.37–6; Table 3). Remarkably, the higher incidence of long-term respiratory impairment in the ABVD cohort was not directly related to the increased bleomycin dose used in this therapeutic regimen. The bleomycin dose received by patients with a detected respiratory impairment was not higher than that administered to patients who did not develop respiratory dysfunction.

Discussion

Hodgkin lymphoma has become a curable malignancy in the vast majority of patients. Broad application of the ABVD

Table 2 Characteristics of patients who developed long-term respiratory impairment

Pt No	Age (yrs)	Sex	Medical history		HL treatment details				Respiratory assessment			
			Smoking history	Previous lung disease	Treatment protocol	Bleomycin accumulative dose (mg/m^2)	RTx dose (cGy)	BPT	Symptoms	DLCO (%)	TLC (%)	VC (%)
1	26	f	No	No	ABVD	120	2700	No	–	68	N	N
2	27	m	No	No	BEACOPP (2×EB+4×SB)	60	0	No	Functional dyspnea	63	N	N
3	30	m	No	No	BEACOPP (6×SB)	60	2500	Yes	–	65	N	N
4	30	m	Yes	No	ABVD	80	0	Yes	–	70	N	75
5	33	m	Yes	No	ABVD	80	2520	No	–	61	N	N
6	46	f	Yes	No	BEACOPP (6×SB)	60	0	No	–	63	N	N
7	45	f	No	No	BEACOPP (6×SB)	60	2700	No	–	69	N	N
8	35	m	No	No	BEACOPP (2×SB+4×EB)	60	4320	No	Functional dyspnea	46	69	61
9	52	m	Yes	No	ABVD	120	2520	Yes	Functional dyspnea	63	N	N

BPT bleomycin pulmonary toxicity; *DLCO* diffusing capacity of carbon monoxide; *N* normal; *RTx* radiotherapy; *TLC* total lung capacity; *VC* vital capacity, *EB* escalated BEACOPP, *SB* standard BEACOPP

Table 3 Risk factors for long-term respiratory impairment

	All *N*=66	Abnormal *N*=9	RR	CI	P
Age					
<30	20	2(10%)			N.S
30-49	33	6(18%)	2	0.36–11	
>50	13	1(8%)	0.75	0.06-9.2	
Gender					
Male	40	6(15.0%)	1.35	0.37–6	N.S
Female	26	3(11.5%)			
Smoking					
Yes	23	6(13%)	1	0.21–4	N.S
No	43	3(14%)			
Previous BPT					
Yes	4	3(75%)	28	2.5–313	0.007
No	62	6(10%)			
Treatment related infection					
Yes	4	1(25%)	2.25	0.20–24	N.S
No	62	8(13%)			
Therapy protocol:					
ABVD vs	21	4(19%)	1.9	0.45–7.8	N.S
BEACOPP	45	5(11%)			
Mantle radiation					
Yes	33	6(18%)	2.22	0.50–9.7	N.S
No	33	3(9%)			
Bleomycin dose					
60-80	53	7(13%)	1.2	0.2–6.5	N.S
100-120	13	2(15%)			

RR relative risk, *BPT* bleomycin pulmonary toxicity

regimen, and more recently, the BEACOPP protocol, has led to essential progress in the outcome of HL patients, with a 10-year progression-free survival and OS of up to 80% and 86%, respectively [2]. Such remarkable survival rates highlight the need to address the issue of preventing long-term sequels in these young subjects. HL therapy is known to be associated with the development of respiratory toxicity [8]. Acute and subacute bleomycin pulmonary toxicity, observed in approximately 20% of patients receiving ABVD, has been suggested to significantly elevate the treatment-related mortality and decrease the survival rate [5–8]. Older age (>40 years), smoking, a previously existing lung or renal impairment, mantle field radiotherapy, and granulocyte colony-stimulating factor (G-CSF) treatment were found to further increase the risk for BPT [8]. The low incidence of BPT in our series, approaching 6% (n=4), may be attributable to the high number of patients treated with BEACOPP, in whom the occurrence of BPT was sevenfold lower than that recorded in patients receiving ABVD (p= 0.000). The incidence of BPT in the ABVD cohort, where prophylactic dexamethasone was administered prior to bleomycin, was similar to that reported in previous series (14%) [7, 8, 19], suggesting a single dose of dexamethasone to be insufficient for preventing BPT in patients receiving the "ABVD bleomycin dosage" [20]. The remarkably low BPT severity observed in these subjects may imply that this "steroid prophylactic" approach could be potentially efficient in reducing the BPT degree.

Notably, despite the concurrent administration of potentially "pulmonary-toxic" drugs as part of the BEACOPP regimen (bleomycin, procarbazine [21], etoposide [22], and G-CSF, increasing the risk of BPT), the incidence of BPT in patients receiving this regimen was very low, approaching 2% only. A similar combination therapy called BEAGOPP, in which etoposide was substituted with gemcitabine, was shown to significantly increase that risk (30%), emphasizing the impact of drug interaction on therapy-related toxicities [23].

The low frequency of BPT observed in patients treated with BEACOPP is most probably attributable to the smaller dose of bleomycin administered in this regimen. Furthermore, the BEACOPP regimen contains a relatively high steroid dose, administered sequentially over a longer period, suggesting this steroid regimen to be more efficient in preventing BPT.

In contrast to the vast data on therapy-related acute and subacute respiratory toxicity, there is a paucity of studies analyzing long-term respiratory complications in the new therapeutic era. A previous trial, one of the very few in this field, in which 51 patients underwent pulmonary function

tests at 3.9 years post-MOPP/ABVD (a relatively "historical" therapy), revealed a reduced diffusion capacity in 7.8% of patients [4]. Studies exploring the impact of modern therapeutic regimens, such as BEACOPP, on long-term respiratory complications, are extremely rare.

In our series, including 21 "ABVD and 46 "BEACOPP" patients, the incidence of a symptomatic long-term respiratory dysfunction was 4.4% (n=3) only. These patients experienced grade I functional dyspnea, associated with a decreased DLCO (n=3) and reduced VC (n=1) or TLC (n=1). Lung function tests revealed an occult respiratory dysfunction in six more patients, suggesting a 13.4% risk for chronic lung impairment in patients treated with ABVD or BEACOPP.

The follow-up duration for patients in the ABVD cohort was shorter than for patients treated with BEACOPP (49 vs. 66 months), which may theoretically contribute to the observed higher incidence of chronic lung impairments in the ABVD group, assuming that the damage could be attenuated over time. However, given the long enough duration of the follow-up of the ABVD patients, approaching 5 years, the chances for respiratory improvement turn out to be low.

The univariate analysis, looking at potential risk factors for long-term respiratory impairment, found a previous history of bleomycin pulmonary toxicity to be the only statistically significant factor (75% vs. 10%, p=0.007, RR=28, 95% CI 2.5–313; Table 3). However, the incidence of abnormal lung function tests tended to be higher in male subjects, patients receiving mantle field irradiation, subjects experiencing respiratory infection while receiving chemotherapy, and those treated with ABVD (Table 3).

Our difficulty to detect statistically significant risk factors for long-term respiratory impairment apart from previous BPT is in all likelihood attributable to the small number of patients analyzed, rather than to the bias effect caused by missing information associated with the retrospective nature of the study or to the lack of lung function tests at treatment initiation. Actually, the data on the majority of patients (76%) were collected prospectively since these subjects participated in the NCT 305149 study where the treatment protocol, chemotherapy dosage, therapy-related complications, and outcome were recorded. Hence, these findings are considered complete and reliable. The lack of direct correlation between the accumulated bleomycin dose and the risk for a chronic respiratory dysfunction appears to reflect the fact that only a minority of patients in our cohort received a medication dose higher than 80 mg/m^2.

Another potential limitation of the study is the lack of "baseline lung function tests" performed prior to the administration of chemoradiotherapy. However, given the young age of the participants and absence of a preexisting lung disease (based on patients' records and CRFs), we assume that the frequency of abnormal lung function tests prior to therapy was extremely low. Therefore, the 13.4% incidence of respiratory impairment observed at 6 years posttreatment is likely to reflect a true, acquired treatment-related toxicity. However, this chronic respiratory impairment was clinically minor, suggesting current therapies to be relatively safe.

Previous history of BPT appeared to be associated with a remarkably high risk for long-term respiratory impairment, emphasizing the need for preventing this treatment-related complication. Indeed, the BEACOPP regimen, where the bleomycin dose is reduced, is associated with a significantly lower risk for BPT compared with ABVD. Furthermore, several studies, where bleomycin was preemptively discontinued, reported a non-inferior outcome in study participants [8]. The UK NCRI–Nordic Lymphoma Study Group (RATHL trial) and the German Study Group are currently investigating whether the bleomycin dose can be significantly reduced or even omitted in patients with advanced and early disease, respectively, aiming to decrease treatment-related toxicity. BEACOPP appears to be "respiratory safer" than ABVD; however, reduction of long-term respiratory complications in HL survivors remains one of the crucial issues that need to be tackled.

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References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ (2009) Cancer statistics, 2009. CA Cancer J Clin 59:225–249
2. Engert A, Diehl V, Franklin J, Lohri A, Dorken B, Ludwig WD, Koch P, Hanel M, Pfreundschuh M, Wilhelm M, Trumper L, Aulitzky WE, Bentz M, Rummel M, Sezer O, Muller-Hermelink HK, Hasenclever D, Loffler M (2009) Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. J Clin Oncol 27:4548–4554
3. Noordijk EM, Carde P, Dupouy N, Hagenbeek A, Krol AD, Kluin-Nelemans JC, Tirelli U, Monconduit M, Thomas J, Eghbali H, Aleman BM, Bosq J, Vovk M, Verschueren TA, Peny AM, Girinsky T, Raemaekers JM, Henry-Amar M (2006) Combined-modality therapy for clinical stage I or II Hodgkin's lymphoma: long-term results of the European Organisation for Research and Treatment of Cancer H7 randomized controlled trials. J Clin Oncol 24:3128–3135
4. Chow LM, Nathan PC, Hodgson DC, Jenkin D, Weitzman S, Grant RM, Manson D, Bross A, Doyle JJ, Danjoux C, Greenberg ML (2006) Survival and late effects in children with Hodgkin's lymphoma treated with MOPP/ABV and low-dose, extended-field irradiation. J Clin Oncol 24:5735–5741
5. Sleijfer S (2001) Bleomycin-induced pneumonitis. Chest 120:617–624

6. Duggan DB, Petroni GR, Johnson JL, Glick JH, Fisher RI, Connors JM, Canellos GP, Peterson BA (2003) Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. J Clin Oncol 21:607–614
7. Lewis BM, Izbicki R (1980) Routine pulmonary function tests during bleomycin therapy. Tests may be ineffective and potentially misleading. JAMA 243:347–351
8. Martin WG, Ristow KM, Habermann TM, Colgan JP, Witzig TE, Ansell SM (2005) Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. J Clin Oncol 23:7614–7620
9. Dann EJ, Bar-Shalom R, Tamir A, Haim N, Ben-Shachar M, Avivi I, Zuckerman T, Kirschbaum M, Goor O, Libster D, Rowe JM, Epelbaum R (2007) Risk-adapted BEACOPP regimen can reduce the cumulative dose of chemotherapy for standard and high-risk Hodgkin lymphoma with no impairment of outcome. Blood 109:905–909
10. Hasenclever D, Diehl V (1998) A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med 339:1506–1514
11. Borg GA (1982) Psychophysical bases of perceived exertion. Med Sci Sports Exerc 14:377–381
12. Fletcher CM (1952) The clinical diagnosis of pulmonary emphysema; an experimental study. Proc R Soc Med 45:577–584
13. Fletcher CM, Elmes PC, Fairbairn AS, Wood CH (1959) The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. Br Med J 2:257–266
14. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J (2005) General considerations for lung function testing. Eur Respir J 26:153–161
15. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J (2005) Standardisation of spirometry. Eur Respir J 26:319–338
16. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, Casaburi R, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson D, Macintyre N, McKay R, Miller MR, Navajas D, Pellegrino R, Viegi G (2005) Standardisation of the measurement of lung volumes. Eur Respir J 26:511–522
17. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, Gustafsson P, Hankinson J, Jensen R, McKay R, Miller MR, Navajas D, Pedersen OF, Pellegrino R, Wanger J (2005) Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 26:720–735
18. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J (2005) Interpretative strategies for lung function tests. Eur Respir J 26:948–968
19. Kimura I, Onoshi T, Kunimasa I, Takano J (1972) Treatment of malignant lymphomas with bleomycin. Cancer 29:58–60
20. Jensen JL, Goel R, Venner PM (1990) The effect of corticosteroid administration on bleomycin lung toxicity. Cancer 65:1291–1297
21. Mahmood T, Mudad R (2002) Pulmonary toxicity secondary to procarbazine. Am J Clin Oncol 25:187–188
22. Williams SD, Birch R, Einhorn LH, Irwin L, Greco FA, Loehrer PJ (1987) Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. N Engl J Med 316:1435–1440
23. Bredenfeld H, Franklin J, Nogova L, Josting A, Fries S, Mailander V, Oertel J, Diehl V, Engert A (2004) Severe pulmonary toxicity in patients with advanced-stage Hodgkin's disease treated with a modified bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone, and gemcitabine (BEACOPP) regimen is probably related to the combination of gemcitabine and bleomycin: a report of the German Hodgkin's Lymphoma Study Group. J Clin Oncol 22:2424–2429