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ORIGINAL ARTICLE

Weight and body composition changes during R-CHOP chemotherapy in patients with non-Hodgkin's lymphoma and their impact on dose intensity and toxicity

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Summary

Purpose: *To estimate weight and body composition changes during R-CHOP combination therapy in patients with non-Hodgkin's lymphoma (NHL) and their impact on dose intensity (DI) and toxicity.*

Methods: *We prospectively evaluated body composition in patients with NHL before starting chemotherapy (visit 1), before the 3rd cycle (visit 2) and before the 6th cycle (visit 3). Body composition was assessed by bioelectrical impedance analysis (BIA) and confirmed by anthropometric measurements.*

Results: *Thirty patients with NHL were studied. There was no weight change from visit 1-2, but weight increased from visit 2-3 (-1.36± 1.89 kg) and from visit 1-3 (-1.93±3.21 kg). Patients with weight gain had significantly better overall response rate (p=0.013) and 5-year survival rate (p <0.01). Fat mass increased from visit 1-2 (-1.068±1.72 kg; p=0.002), from visit 2-3 (-1.32±1.89 kg; p=0.001) and from visit 1-3 (-2.502±3.23 kg; p=0.001). There was no statistically significant change in lean body mass (LBM) during chemotherapy. Total body water changed significantly from visit 1-2 (-0.08±2.55l kg; p=0.097), from visit 2-3 (-1.036±1.10 kg; p=0.001) and from visit 1-3 (-1.89±3.2l kg; p=0.004).*

The average relative DI (ARDI) of the R-CHOP regimen was 90% and the rate of complete remission was 63.3%. Overall hematologic toxicity was evident in 14 (46.7%) patients. There was statistical significance between concentrations of cyclophosphamide and doxorubicin (mg/kg fat and mg/kg LBM) whether overall hematologic toxicity was present or not.

Conclusion: *Patients in the study gained weight during chemotherapy with unfavorable changes in body composition. Attempt has been made to identify clinical variables to predict patients at risk for hematologic toxicity, but an approach for individualizing drug dosing should be continued.*

Key words: body composition, body weight, dose intensity, non-Hodgkin's lymphoma

Introduction

Weight loss is a well recognized problem in cancer patients and has been shown to be an independent prognostic indicator of decreased survival, and leads to changes in the body compartments [1,2]. Cancer cachexia is seen in most patients with advanced cancer of the stomach, pancreas, lung and colon. In contrast, tumors such as breast cancer and hematologic malignancies are rarely associated with cachexia. Patients with identical primary cancer and disease stage can vary in terms of cachexia development, suggesting variations in tumor phenotype and host response. Common changes for all patients are loss of fat mass and skeletal muscle mass [3-7].

There are many techniques for body compartment analysis that are based on various assumptions. BIA is a safe, rapid, noninvasive, reproducible, bedside technique that measures total body fat mass, LBM and body water. The method relies on the conduction of a low voltage alternating current through the body. Measurement of the voltage drop, together with information on patient height, weight, age and gender serve in equations for multiple regression relationship to predict body composition [8,9]. Its main limitation is the lack of a standard norm in cancer patients but it has similar accuracy for the prediction of body composition to the anthropometric tests [10]. It is easy to predict body composition as two-compartment model (fat mass and fat free mass) using measurements of 4 sides skin fold thickness [11].

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The prognostic effect of weight loss prior to chemotherapy was recognized more than 50 years ago. In the study of DeWys et al.[1], the frequency of weight loss ranged from 31% for favorable NHL to 87% in gastric cancer, using data from 3,047 patients receiving 12 chemotherapy regimens. Median survival and chemotherapy response rates are shorter in patients with weigh loss. Decreasing weight was correlated with decreasing performance status that is a recognized prognostic factor in lymphomas which affects response to chemotherapy and duration of survival [12]. Reasons for weight loss are specific tumor-host interactions and *vice versa,* together with recently understood patient factors like age, level of physical activity, and the specific patterns of protein metabolism in cancer patients [1].

Most of the authors agree that weight loss in cancer patients is due to decrease of fat mass [3-5]. Shizgal [6] found that these patients loose in fat compartment while LBM could decrease or stay unchanged. LBM is unchanged if there are unfavorable changes - decrease in body cell mass and increase in extracellular water [6].

It is well known that CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) combination chemotherapy is one of the least toxic NHL therapeutic regimens. Interpatient variations in toxicities could arise from differences in drug metabolism, excretion, physiologic and genetic factors. Also, heterogeneous body composition, and especially, relative amounts of lean and adipose tissue compartments contribute to it. The size of these compartments relate to the pharmacokinetic properties of a drug, as hydrophilic drugs distribute into the lean compartment and lipophilic drugs distribute into the fat compartment. Dosing of drugs based on body surface area (BSA) became established in clinical settings in part by dogma, and not due to studies showing that interpatient pharmacokinetics variations correlated to it [13,14].

There is growing evidence to suggest that LBM may be a better alternative for normalizing doses of drugs that are distributed and metabolized in this compartment. LBM compartment comprizes metabolic tissues, such as the liver and kidney, and intracellular and extracellular water and bone [15-17].

In an attempt to clarify how weight and body composition change in patients receiving rituximab (R)-CHOP, we prospectively evaluated weight and body composition of patients with NHL before starting and during treatment, and compared these findings with response to therapy and 5-year survival. Also, the DI of R-CHOP was analyzed. Hematologic toxicity was assessed, related to concentrations of cyclophosphamide and doxorubicin of LBM and fat mass.

Methods

Patients

Thirty patients with NHL were recruited between June 2001 and August 2002. Patients were included in the study if they had immunopathologically confirmed NHL and were planned to receive R-CHOP chemotherapy [21-day cycle, at standard doses: rituximab 375 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 750 mg/m^2, vincristine 2 mg max (day 1) and prednisone 100 mg p.o. (days 1-5)]. The disease stage was defined according to Ann Arbor staging system. Patients were stratified in different risk groups according to International Prognostic Index score [12]. Patients were excluded if they had history of liver, kidney or heart failure because of possible interference with the BIA method. The study was closed in June 2008.

Estimation of body composition

Patients with NHL were prospectively evaluated on 3 occasions: at baseline, before the 3rd, and before the 6th chemotherapy cycle. During each visit, the patients were weighed to the nearest 0.01 kg using an electronic scale that was calibrated (against a standard weight) before each measurement. Height was measured to the nearest 1 mm with a stadiometer. Skinfold thickness was measured with Harpenden caliper (British Indicators Ltd, Albans, Herts) to the nearest mm, except low valued (usually 5 mm or less) when it was taken to the nearest 0.5 mm. Readings were made at 4 sites in all subjects: at the biceps, triceps, subscapular and supra-iliac areas. These were usually done on the right side of the body with the subject standing in a relaxed position. Fat percentage was read in the original scale of Durnin [5]. Measurement of body impedance was taken with subjects supine (socks and shoes removed) on hospital beds, when relaxed, without diuretics and alcohol consumption 24 h and coffee 4 h before testing, 2-3 h after meal. Maltron Analyser Model BF-905 (Maltron Limited, Rayleigh, Essex, United Kingdom) was used (electrical current 800 microA and frequency of 50 KHz).

Dose intensity

Actual chemotherapy doses were available for all 30 patients. The method of Hryniuk and Bush [18] was used to calculate the DI of each drug actually administered to the patients. DI was expressed as a decimal fraction of the dose prescribed in a standard regimen over the same time frame (relative DI, RDI). The following assumptions were made in calculating actual RDI: 1) a

maximum value of 1.00 was allowed to the RDI of prednisolone since no clear dose-response relation exists for steroids given in therapeutical doses; 2) the capping off of vincristine doses at 2.0 mg in all patients gives the actual RDI value 1.00. By summing RDIs of all agents included in a regimen and dividing this sum by the number of agents used, ARDI is calculated.

The usual situation is that drug regimen doses stay the same throughout therapy (calculated as mg of drug/m^2 BSA at presentation). Since it is known that patients change their weight during treatment it is expected that their BSA also changes. For all patients the projected DIs were calculated considering their changes in BSA after treatment.

Toxicity assessment

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0. Assessment of hematologic toxicity was based on blood counts before each chemotherapy cycle, defined as overall toxicity (any grade 3/4 toxicity, dose delay or dose reduction) and compared with body composition parameters.

Statistical analysis

For statistical analysis, patients were stratified in groups with indolent or aggressive lymphoma.

The distribution of each demographic and clinical variable was reviewed, and appropriate summary measurements were estimated, including means, medians, and proportions. Group comparison was based on chi-square distributions for categorical variables, and those for continuous variables were based on Student's t test for normally distributed variables and Mann-Whitney statistics for all other variables. Two-sided tests of the null hypothesis were used throughout. Statistical programme SPSS (Chicago, for Windows, version 11.5) was used.

Results

Patient characteristics

There were 12 men and 18 women, aged between 20 and 82 years (median 56). Fifteen patients were with indolent and 15 with aggressive lymphoma, according to Working Formulation. Median patient age with indolent and aggressive NHL was similar (56 vs. 58 years, respectively, p=0.832).

No significant difference in the proportion of patients older than 60 years, presence of B symptoms, Karnofsky index, clinical stage (>2), number of extranodal localizations, splenomegaly, or IPI score was observed. Weight loss >10% at the time of diagnosis was noted in 46.7% of patients, with greater incidence in those with aggressive lymphoma (66.7%; p=0.028). Bulky disease at presentation was more frequent in patients with aggressive lymphoma (p=0.025). Weight loss prior to chemotherapy (in all patient, no matter which lymphoma type) was evident in patients with disseminated disease (clinical stage >2; p=0.013).

Patients were treated with different number of chemotherapy cycles: 15 patients with 6 cycles, 7 with 8 cycles and 5 with 9 cycles. There were 40% complete responses (CR), 46.7% partial responses (PR), 10% progressive disease (PD) and 3.3% deaths after the 6th chemotherapy cycle. At the end of treatment (after the 9th cycle), there were 63.3% CR, 16.7% PR, 10% PD and 10% deaths. The difference in treatment results (after 6 and after 9 chemotherapy cycles) was statistically significant (p <0.05).

Three patients died during therapy: the first death was due to heart failure; the second to cerebrovascular accident; and the third to hepatic insufficiency. After 5-years follow up, 17 (56.7%) patients were alive, 11 (36.7%) had died, and 2 patients were lost to follow up. The main cause of death was relapsed or resistant disease.

Comparison of weight changes during chemotherapy

Weight changes (visit 1-3) and overall, response rate are outlined in Table 1. Among 30 patients, 9 lost weight (median –3 kg, range: –1 to –5), 17 gained weight (median +3 kg, range: +1 to +4), and in 4 patients weight remained unchanged, between visit 1-2. The mean weight between visit 1-2 showed a small, nonsignificant decline (69.53±14.22 kg to 69.97±13.97 kg; -0.43±2.097 kg; p=0.267). Between visit 2-3, 8 patients lost weight (median –1 kg, range: +1 to +2), and 22 gained weight (median +3 kg, range: +1 to +5). Mean weight between visit 2-3 increased significantly (70.25±14.22 kg;

Table 1. Weight changes (visit 1-3) and overall response rate

Weight change	*CR, PR, SD n (%)*	*PD, death n (%)*	*p-value*
Gain	18 (94.7)	1 (5.3)	0.013
Decrease	3 (42.9)	4 (57.1)	
No change	3 (75)	1 (25)	
Total	24 (80)	6 (20)	

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease

71.61±14.75 kg; –1.36±1.89; p=0.001). Over the entire 6 cycles of chemotherapy, 19 patients gained weight (median +3 kg, range: +1 to +8), 7 patients lost weight (median –2 kg, range: –1 to –4), and in 4 weight showed no change. There was significant increase in weight (–1.93±3.21 kg; p=0.004) from visit 1-3.

Patients who gained weight during chemotherapy had significantly better response rate (p=0.013). Also, patients who gained weight during chemotherapy had significantly better 5-year survival (p <0.01; Table 2).

Changes of body composition during chemotherapy

Anthropometric measurement of fat mass highly correlated with fat mass measured by BIA method (r=0.996, p <0.01). Measurements by BIA method are presented in the Table 3.

BIA percentage of body fat showed upward trend throughout the chemotherapy period, and this difference was statistically significant. Namely, mean increase from visit 1-2 was –1.07±1.72 kg (p=0.002); from visit 2-3 it was –1.32±1.89 kg (p=0.001); and from visit 1-3 it was –2.5±3.23 kg (p=0.001). However, there was no difference between fat mass and overall response rate. Also, there was not statistically significant difference in fat mass between patients who had or not significant weight loss prior to chemotherapy (p=0.330).

BIA percentage of LBM showed downward trend during chemotherapy, but this difference was not statistically significant. Mean decrease from visit 1-2 was 0.56±1.65 kg (p=0.071); from visit 2-3 it was 0.04±1.14 kg (p=0.867); and from visit 1-3 it was 0.57±1.95 kg (p=0.133). There was no difference between LBM and overall response rate, and 5-year survival. There was no difference in LBM between patients with or without significant weight loss prior to chemotherapy (p=0.304).

Total body water showed small but significant increase during chemotherapy (between visit 2-3 and 1-3). The mean increase from visit 1-2 was 0.8±2.55 kg (p=0.097); from visit 2-3 it was –1.04±1.10 kg (p=0.001); and from visit 1-3 it was –1.89±3.20 kg (p=0.004).

The changes of body compartments occurred irrespective of age or sex.

Dose intensity

RDI for cyclophosphamide was 81.2±18%, and for doxorubicin it was 80.8±16.8%. There was no difference in RDI of both drugs considering the age of the patients (younger vs. older than 60 years).

In patients with complete and partial response to therapy RDI for cyclophosphamide was 81% (min 21%, max 106.3%). In these patients, doxorubicin RDI was 82% (min 40%, max 108.8%). In the group of patients

Table 2. Weight changes during chemotherapy and 5-year survival

Weight change	*Alive n (%)*	*Dead n (%)*	*p-value*
Gain	16 (84.2)	2 (10.5)	<0.01
Decrease	1 (14.3)	6 (85.7)	
No change	–	3 (75)	
Total	17 (56.7)	11 (36.7)	

Table 3. Measurements by bioelectric impedance analysis method

		Patients, n	*Min*	*Max*	*X, median*	*SD*	*p-value*
Fat % and kg	visit 1	30	10.8%	38.3%	25.72%	7.82	<0.01
			7.0 kg	41.6 kg	18.32 kg	8.16	
	visit 2	30	14.9%	43.8%	27.13%	7.53	
			10.0 kg	42.6 kg	19.38 kg	8.07	
	visit 3	28	18.1%	43.6%	28.29%	7.61	
			11.0 kg	46.7 kg	20.95 kg	8.77	
LBM % and kg	visit 1	30	61.7%	89.2%	74.55%	7.47	>0.05
			34.0 kg	69.0 kg	51.21 kg	9.33	
	visit 2	30	56.1%	85.1%	73.0%	7.31	
			32.0 kg	70.0 kg	50.64 kg	9.41	
	visit 3	28	58.9%	81.9%	71.89%	7.14	
			33.0 kg	71.0 kg	50.66 kg	9.25	
Water % and kg	visit 1	30	43.6%	70.0%	57.97%	5.98	<0.05
			24.0 kg	61.0 kg	39.97 kg	7.74	
	visit 2	30	47%	70.0%	58.81%	5.15	
			29.0 kg	63.0 kg	40.77 kg	7.33	
	visit 3	28	48%	68.0%	58.99%	4.94	
			30.0 kg	65.0 kg	41.93 kg	7.89	

LBM: lean body mass, SD: standard deviation

without response to therapy RDI for cyclophosphamide was 80% (min 49.6%, max 96.6%) and for doxorubicin RDI 77.7% (min 52.1%, max 96.5%). The difference between groups was not statistically significant (Table 4).

ARDI was between 68-101%. There was no difference in ARDI and response to therapy. In both groups (responders and non responders) ARDI was 90%.

There was no statistical difference in the drugs' dosing comparing to mathematically derived drug dosage considering body mass changes during chemotherapy.

Toxicity

Evident changes in chemotherapeutic drug concentrations in body compartments considering changes in body composition during chemotherapy were found (Table 5). Statistical significance existed between cyclophosphamide and doxorubicin concentrations in the fat compartment (p=0.012 and p=0.038, respectively) and their concentrations in water compartment (p=0.019 and p=0.019, respectively).

The most frequent hematologic toxicity was leucopenia which was reason of treatment delay in 62.1% of cycles. Overall hematologic toxicity was evident in 14 patients. There was no difference in toxicity between genders (p=0.296). Although it was more frequent in older patients (61 vs. 39%) the difference was not statistically significant (p=0.796).

There was statistical significance between concentrations of cyclophosphamide and doxorubicin (mg/kg fat and mg/kg LBM) whether overall hematologic toxicity was present or not (Table 6).

Table 4. Relative dose intensity (RDI) of drugs and average relative dose intensity (ARDI) in patients with and without response to therapy

	CR+PR	*SD+PD+death*	*p-value*
RDI cyclophosphamide	81.4±18.4%	80±17.7%	0.878
RDI doxorubicin	81.59±17.1%	77.7±16.5%	0.663
ARDI	90.28±8.1%	89.47±3.7%	0.853

For abbreviations see footnote of Table 1

Table 5. Drug concentrations (mg/kg) before the 1st and 6th therapy cycle

	Therapy cycle	*Cyclophosphamide X median±SD*		*Doxorubicin X median±SD*	
Fat (mg/kg)	1	80±37.39	p=0.012	4.9±2.1	p=0.038
	6	68±24.54		4.29±1.42	
LBM (mg/kg)	1	24.9±4.85	p=0.469	1.62±0.28	p=0.885
	6	25.4±5		1.6±0.31	
Water (mg/l)	1	31.7±6.3	p=0.019	2±0.38	p=0.019
	6	30.4±6.25		1.9±0.37	

LBM: lean body mass, SD: standard deviation

Discussion

Decreasing weight was correlated with decreasing performance status which is recognized as prognostic factor in lymphomas regarding response to chemotherapy and duration of survival [12]. Significant weight loss (>10% of body mass in 6 months) was found in nearly half of the NHL patients, particularly in disseminated disease (clinical stage >2) and in aggressive subtypes of NHL. In this study, patients with weight loss prior to chemotherapy had equal therapeutic response as patients without weight loss prior to chemotherapy. Also, there was no difference in body fat and LBM between patients with or without significant weight loss prior to chemotherapy.

Changes in body composition and weight gain during chemotherapy, particularly during adjuvant treatment of breast carcinoma, have been previously reported [19-21]. Uncontrolled trials have suggested that significant increases in weight occur in 50-96% of all early-stage breast cancer patients during adjuvant chemotherapy, with median gain in weight, ranging from 2.5 to 6.2 kg during treatment and follow up periods up to one year [19,20], and unfavorable changes in body composition [21]. The specific reason is not clear but factors such as glucocorticoids in therapy, reduction in physical activity, excessive food intake could contribute to this observation.

Changes in weight and body composition in adult patients with NHL during chemotherapy were not reported yet. However, few studies about body composition changes were done in survivors of childhood hematological malignancies (lymphoma and acute leucemia) [22,23].

Although, the number of patients in this study was

Table 6. Drug concentrations (in fat and lean body mass) and overall hematologic toxicity

	Overall hematologic toxicity X median±SD		*p-value*
	Present	*Absent*	
Fat (mg/kg)			
Cyclophosphamide	77.9±25.1	54.81±17.07	0.011
Doxorubicin	4.9±1.5	3.5±0.78	0.008
LBM (mg/kg)			
Cyclophosphamide	27.23±2.5	22.89±6.4	0.02
Doxorubicin	1.71±0.32	1.5±0.28	0.077

LBM: lean body mass, SD: standard deviation

relatively small, the main advantage was the precise selection of chemotherapy model, the longer follow up post-completion of chemotherapy, and the comprehensive anthropometric and associated assessments.

NHL patients in this study gained weight during chemotherapy. The interesting point is that patients with better response to therapy gained weight comparing to those in whom disease progressed. Also, almost all patients who gained weight during chemotherapy were alive after 5 years of follow up. However, these weight changes could be explained by changes in body compartments. There was a significant upward trend in fat mass between every measurement point. The downward trend of LBM was not statistically significant but accompanied changes in the fat compartment. Body water changes showed small but significant upward trend.

DI is a measure of total dose of chemotherapy delivered over time. There is increasing evidence that maintaining DI increases the disease free and overall survival in patients with NHL [24-26]. Lepage at al. [25] reported that RDI of doxorubicin greater than 75% was shown as the single most important predictor of survival. Moreover, elderly patients who received doxorubicin at DIs ≥ 10 mg/m^2 per week had outcomes (5-year survival) that were comparable to those of young patients [26]. In our study all patients received more than 75% RDI regardless of age. In the randomized studies of Hagberg et al. [27] (0.32 ARDI and 61% CR) and Gams et al. [28] (0.29 ARDI and 43% CR) it was shown that remission rates are achieved if the patients receive higher regimen DIs. In our study ARDI was 90% with 63.3% CR; these results are in accordance with previous studies [29].

Randomized clinical trials of CHOP, R-CHOP, and CNOP have consistently reported that myelosuppression in general and neutropenia in particular represent the major dose-limiting toxicity. In our study neutropenia was the reason for treatment delays in 62% of the cycles. After administration, a chemotherapeutic drug is distributed in body compartments. With changing size of body compartments during disease and its therapy it will be of great importance to deliver individualized doses depending on the compartment size. The best predictor of drug dosing is LBM compartment [15,16]. Prado et al. [17] found that small LBM compartment is significant predictor of toxicity in women treated with 5-FU. In this study it was shown that there was significant difference in drug concentrations (mg/kg fat and LBM) between the 1st and 6th cycle of chemotherapy.

We conclude that patients in this study gained weight (positive prognostic factor), but this change was unfavorable in the light of body compartments. There was gain in fat mass and body water, but loss in LBM compartment. DI study was similar to earlier investigations. Attempt has been made to identify clinical variables to predict patients at risk for hematologic toxicity, but an approach for individualizing drug dosing should be continued. Further studies delineating subsequent weight change in NHL patients who are followed up for long periods of time are needed to determine physical and metabolic effects of these body composition changes.

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