

Predictive Factors of Response to Decongestive Therapy in Patients with Breast-Cancer-Related Lymphedema

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ABSTRACT

Background. Many studies have reported the benefits of Decongestive treatment in patients with breast-cancer-related lymphedema (BCRL) but few have study what are the predictive factors of response.

Methods. We performed a prospective, multicenter controlled cohort study of 171 patients with BCRL to identify independent predictive factors of response to decongestive treatment (CDT). Demographic data and clinical and lymphedema characteristics were collected prospectively. The end point was the “percentage reduction in excess volume (PREV).” Volumes were measured prior and at the end of CDT. Factors associated with response (PREV) were tested in univariate and multivariate analyses using linear regression techniques.

Results. Median age was 60.4 years (range 32–84); mean lymphedema chronicity 4 years [95% confidence interval (95% CI): 3.1–5.0]; mean baseline excess volume (EV) was 936 mL (95% CI: 846–1026), and mean percentage EV was 35.3% (95% CI: 32.0–38.7); compliance to bandages was good in 81.3% of patients. PREV was 71.7% (95% CI: 65.2–78.2). After univariate screening, 11 variables were found to be associated with PREV but only 4 variables were independent predictive factors of response to CDT in the multivariate analysis: Venous insufficiency, percentage of EV (the higher the EV, the lower the reduction with CDT); compliance to bandages (a good compliance improved PREV in 25%), and treatment in autumn (better results than during the rest of the year).

Conclusions. This study shows that compliance to bandages during CDT is one of the most important predictors of response. Moreover, data support the idea that more severe lymphedemas have a worse response to treatment, and it should be recommended in early stages. The association between the season of treatment and response was also very strong, so weather conditions are an additional factor that must be taken into account in further studies.

Lymphedema, defined as the abnormal accumulation of protein-rich fluid in soft tissues, results from a dysfunction of the lymphatic system.¹ In the case of breast-cancer-related lymphedema (BCRL), it develops when lymph transport is impaired due to damage or resection of lymph nodes as a result of surgery and/or radiation.²

The incidence of BCRL ranges from 6% to 56%, depending on different studies, because of the lack of standard diagnostic and assessment criteria.^{3–10} As has been described, BCRL is associated with disability of the arm, with lower levels of quality of life, and with psychological as well as social sequels.^{11–15} Nevertheless, lymphedema has been one of the adverse effects of cancer treatment that has received less attention in the literature.¹⁶ The wide variety of therapies and schedules employed in each center, the lack of uniformity in the insurance coverage of treatments, and the isolation of the research groups further complicate any research in this field.

The “golden standard” of treatment for lymphedema is the complex decongestive treatment (CDT), which includes manual lymphatic drainage, compression with multilayer bandages, exercises, and skin care.¹⁷

Several studies have reported the benefits of CDT in patients suffering BCRL with a reduction in the excess volume between 22% and 73%.^{1,18–21} Some factors have

been found to be associated with the outcome of CDT, namely, the degree of lymph node dissection, patient's weight, history of lymphangitis, and the volume at baseline.^{22–25}

Only one study has identified the body mass index (BMI) and the duration of lymphedema as predictive factors of response to CDT by means of a univariate analysis.²⁶

To our knowledge, there are no published reports of predictive factors of response to CDT using a multivariate analysis. Therefore, the goal of this paper is to identify the independent predictive factors of response to CDT.

PATIENTS AND METHODS

Study Design

We performed a prospective, multicenter-controlled cohort study of patients with BCRL who were treated with decongestive therapy to identify independent predictive factors of response to the treatment using a multivariate analysis.

The performance of the response was evaluated with the “percentage reduction in excess volume (PREV),” which is obtained with the following formula: (Initial EV – Final EV)/Initial EV, where excess volume (EV) is the difference between lymphedematous (VL) and healthy limb volume (VH). Volumes were calculated prior to and at the end of the treatment, with tape perimeter measurements (C) taken from the dorsum of the hand (C_1) and repeated for every 4 cm proximally until the axilla (C_n), using Kuhnke formula, as the disk model is considered the method of choice in clinical practice.^{27–29}

$$\text{Volume} = \frac{C_1^2 + C_2^2 + \dots + C_n^2}{\pi}$$

The percentage of EV (PEV) is the edema relative to the normality that is the healthy limb {PEV = [(VL – VH)/VH] × 100}. This parameter is better for defining the severity of the lymphedema than are the absolute values of volume because of the heterogeneity of the anthropometric measures in the sample.

The following parameters were assessed on entry in the study and evaluated for their predictive value (Table 1): clinical and demographic characteristics (age, weight, BMI), breast-cancer treatment characteristics [type of surgery, number of positive and removed nodes, chemotherapy regimen, drugs, concomitant radiotherapy (RT), RT dose], lymphedema characteristics [percentage of excess volume (PEV); stage, chronicity, dermal complications, history of lymphangitis, symptoms, ...], and CDT characteristics (sessions, season of treatment, compliance to bandages).

All patients received complex decongestive treatment with manual lymphatic drainage, during 45 minutes, pressotherapy with a pneumatic multichambered device (Lymphapress, Mego-Afek AC Ltd., IL) between 50 and 80 mm Hg, during 30 minutes, and multilayered bandages that the patient had to wear until the next day. The sessions were performed by an expert lymphotherapist in consecutive days until a plateau in reduction was reached, normally between 10 and 20 sessions. The tape measurements were taken by another examiner before and at the end of the whole treatment. No drugs were prescribed during decongestive treatment, but previous pharmacologic agents for comorbidities were respected.

Compliance to bandages was registered daily by the physician. The bandages were examined and taken off at the beginning of every new session. The times that the patient arrived without the bandages or had bandaged herself incorrectly was registered. Compliance was considered good when patient maintained the bandages ≥ 90% of the time of treatment, fair between 60% and 89%, and bad <60% of the time.

Patient Selection

From June 2002 to August 2008 patients diagnosed with unilateral BCRL who were scheduled to begin CDT were included in the study. The inclusion criteria were: age more than 18, free of malignant disease, and no CDT for one year. The exclusion criteria were: cardiac disease, non-controlled hypertension, deep-vein thrombosis, active lymphangitis, history of severe arm trauma or surgery, stroke, flaccid paralysis of the arm, and psychological diseases. All the patients agreed to participate in the study and accepted that their clinical data would be treated anonymously for scientific noncommercial purposes.

Diagnosis of lymphedema was made based on clinical exam when perimeter measurement compared with the contralateral limb was >2 cm and the PEV was >10%.

X-ray, duplex ultrasonography, magnetic resonance, and electromyography were used to discard malignancy and other exclusion criteria, when required.

Statistical Analysis

The results of descriptive analysis were presented in terms of central tendency and dispersion (mean, median, 95% confidence interval) for continuous variables, and the absolute and relative frequencies were calculated for categorical variables.

Factors associated with response (PREV) were tested in a univariate and multivariate analyses using linear regression techniques.

TABLE 1 Patient characteristics

Clinical and Demographic Characteristics	
No. of patients	171
Age (median; range)	60.4 (32–84)
Side of upper limb	
Right	82 (48%)
Left	89 (52 %)
Dominance (%)	87 (51.2 %)
Chronicity (years) (mean; 95% CI)	4.0 (3.1–5.0).
Weight (kg) (mean; 95% CI)	76.9 (74.8–79.0)
BMI (mean; 95% CI)	30.4 (29.6–31.2)
Venous insufficiency in lower limbs	30 (17.5%)
Hypertension	61 (35.7%)
Nervous impairment (%)	8 (4.7%)
Limitation in the range of motion (%)	70 (40.9%)
Breast cancer treatment characteristics	
Type of surgery (%)	
Modified radical mastectomy	100 (58.5%)
Quadrantectomy	30 (17.5%)
Lumpectomy	38 (22.2%)
Axillary lymphadenectomy (%)	169 (98.8%)
Number of positive nodes (mean; 95% CI)	2.9 (2.1–3.7)
Number of removed nodes (mean; 95% CI)	16.8 (15.4–18.2)
Type of adjuvant therapy (%)	
Chemotherapy	128 (74.9%)
Radiotherapy	138 (80.7%)
Hormone therapy	122 (71.3%)
Site of radiotherapy	
Breast	65 (38%)
Breast + regional lymphatic nodes	73 (42.7%)
Total dose of radiotherapy (Gy)	47.0 (41.1–52.8)
Lymphedema characteristics	
Lymphedema stage	
II	30 (17.5%)
III	116 (67.8%)
III (elephantiasis)	25 (14.6%)
Absolute volume (mL) (mean, 95% CI)	3615 (3463–3767)
Baseline EV (mL) (mean, 95% CI)	936 (846–1026)
Baseline percentage EV (mean, 95% CI)	35.3% (32.0–38.7)
Baseline heaviness (VAS) (mean, 95% CI)	4.6 (4.0–5.2)
Baseline numbness (VAS) (mean, 95% CI)	2.3 (1.8–2.8)
Dermal complications (%)	68 (39.8%)
History of lymphangitis (%)	69 (40.4%)
Number of episodes of lymphangitis (mean, 95% CI)	1.2 (0.6–1.7)
Fibrosis	
No	91 (53.2%)
Local	55 (32.2%)
Extended	25 (14.7%)
CDT characteristics	
Number of sessions (mean, 95% CI)	16.8 (16.2–17.4)

TABLE 1 continued

Compliance to bandages	
Good ($\geq 90\%$ of the time)	139 (81.3%)
Fair (60–89%)	13 (7.6%)
Bad ($< 60\%$)	13 (7.6%)
Season of treatment (%)	
Winter	59 (34.5%)
Spring	42 (24.7%)
Summer	34 (19.9%)
Autumn	35 (20.5%)

BMI body mass index, EV excess volume, VAS visual analog scale, CDT complex decongestive therapy

Factors for initial inclusion in the model were identified by univariate analysis screening with a P value $< .1$. This is a recommended approach for removing unimportant covariates that ensures a more manageable set of variables that can be analyzed with multivariate techniques.^{30,31} The association between categorical variables and response variable (PREV) was explored by analysis of variance (ANOVA test). The data were also tested for compliance with the requirements for ANOVA that are normality of the data (Kolmogorov-Smirnov test) and homogeneity of variances (Levene's test). If these tests were significant ($P \leq .05$) for any analysis of variance, a nonparametric analysis with Kruskal-Wallis Test was applied. The analysis of the relationship between continuous variables and response variable (PREV) was based on a linear regression model (β coefficient).

In order to determine the final predictive factors for retention in the model, a multivariate linear regression analysis was applied. The presence or absence of confounding factors, multiple effects, and interactions between study variables with the outcome variable were determined using the method described by Kleinbaum.³²

In all cases, hypothesis testing was two-tailed, with the application of a 5% level of significance ($P \leq .05$). The patient database and statistical analyses were made using the SPSS statistical package version 15 (SPSS Inc, Chicago, IL).

RESULTS

Patient Characteristics

A total of 171 patients were included in the study, and all of them were analyzed after enrollment (total population). Table 1 shows the baseline characteristics of the patients. Median age was 60.4 years (range 32–84), mean of BMI was 30.4 kg/m² (95% CI: 29.6–31.2), 87 patients had lymphedema in her dominant arm (51.2%), 67.8%

were stage III, lymphedema chronicity was 4.0 years (95% CI: 3.1–5.0), 40.4% of patients had a lymphangitis history, mean baseline EV was 936 mL (95% CI: 846–1026), and mean percentage of excess volume (PEV) was 35.3% (95% CI: 32.0–38.7).

Compliance to bandages was good in 81.3% of patients. The mean number of physiotherapist sessions was 16.8 (95% CI: 16.2–17.4).

The EV at the end of treatment was 337 mL (95% CI: 286–388) with a mean of reduction of 71.7% (95% CI: 65.2–78.2).

Univariate Analysis

Only 11 variables were retained after initial univariate screening considering all the recorded parameters (Table 2). The presence of venous insufficiency, treatment in autumn, and a good compliance to bandages were associated with a better response.

Higher baseline EV and PEV, heaviness and numbness sensation, chemotherapy administration, radiotherapy of axilla and total dose of RT, and treatment in winter were associated with a lower outcome.

No confounding factors were found between the variables.

Multivariate Analysis

After multivariate linear regression, only four variables were found to be independent predictive factors of response to decongestive therapy: venous insufficiency, percentage of initial excess volume, compliance to bandages, and treatment in autumn (Table 3).

When the patient had a history of venous insufficiency in lower limbs diagnosed by a vascular surgeon by duplex ultrasonography, the percentage of the reduction was more important. When the edema was higher either measured in absolute values or in the relative value “percentage of excess volume,” less reduction was obtained with the treatment. When the compliance to bandages was good, there was a better response than when compliance was poor or just fair.

Finally, the patients treated in autumn obtained higher levels of reduction than those treated during the rest of the year.

DISCUSSION

This study found that a good compliance to the bandages by the patient improved the percentage of reduction of EV by 25% compared with fair or bad compliance, which has not been reported before. Previous studies have reported the important role of low-stretch compression bandages in the reduction of lymphedema volume.^{33–35} The pressure with the bandage is applied by the tissues against the

resistance of the multilayer bandage when the muscles are contracting. The amplitudes between pressures in rest and activity are the base of its efficacy.³³ Pressures are higher when standing and significantly altered during walking.³⁶ Compression can also improve the morphological changes of the skin in chronic lymphedema.³⁷ In addition, it was found that the relative value “percentage of excess volume” is better for evaluating edema evolution than absolute volume measurements.

The local climate has emerged as an important factor related to bandage compliance. Humid and warm weather adds an additional difficulty in the treatment of lymphedema patients. It is very difficult to convince them to wear the multilayer bandages 24 hours between physiotherapy sessions, as most of them receive decongestive therapy in an outpatient regime.

A possible solution to this would be to plan, whenever possible, the treatments during the most convenient season. In the case of this study, (Valencia, Spain) the average weather conditions during the year are typical of Mediterranean climate (mild winters and hot summers). In the warmest month, August, the typical temperature during the day ranges from 26 to 32°C (79–90°F), above 20°C (68°F) at night.

The warm weather and the difficulty in maintaining a normal life are the major complaints and the main reasons of withdrawal. That is the reason to always control the patient’s compliance to the bandages. These are an important part of the therapy as all the systematic reviews recommend them.^{17,19,20,38–40} This study strongly shows that compliance to bandages during decongestive treatment is one of the most important predictors of response. So, if we want to improve the efficacy of the treatment we must convince the patient to comply with the bandages. This can be achieved with clear information of the benefits of bandages, involving the family members to obtain their help at home, informing the general practitioner in order to get the job permissions, and being exigent when including the patient in the treatment, in summary motivating the environment of the patient. In addition, it is also recommended to include some variables in the clinical history to assess the motivation of the patient to follow the therapy, for example, social and education level.

Nevertheless, we found that the season of treatment was an independent predictive factor of response to CDT. The patients treated in autumn obtained better outcome than during the rest of the year. We have observed that after the summer patients show an increase in the volume of their arm due to high summer temperatures and the bad compliance to garments.⁴¹ This edema is probably a recent and nonstructured lymphatic fluid that can be reduced more easily with treatment during autumn when bandages are better tolerated. Although this has not been taken into

TABLE 2 Univariate analysis of variance: Factors associated to response

Factors	ANOVA test (mean; 95% CI)	β coefficient of linear regression (β coefficient; 95% CI)	<i>P</i>
Age		0.05 (−0.50 to 0.59)	.869
Body mass index		0.79 (−0.46 to 2.03)	.213
Dominance			
No	75.5% (64.4–86.6)		.204
Yes	67.1% (60.0–74.2)		
Nervous impairment			
No	72.1% (65.3–78.8)		.554
Yes	62.8% (40.0–85.5)		
Venous insufficiency in lower limbs			
No	65.3% (60.0–70.6)		<.0001
Yes	101.2% (75.1–127.4)		
Range of mobility			
Normal	72.7% (64.5–80.8)		.708
Limited	70.1% (59.2–81.1)		
Chronicity		0.17 (−0.75 to 1.09)	.712
Lymphedema stage			
II	76.4% (52.4–100.4)		.393
III	72.6% (65.2–80.0)		
III elephantiasis	61.2% (53.7–68.7)		
Baseline EV (mL)		−0.02 (−0.03 to −0.01)	<.0001
Percentage of initial EV		−0.73 (−1.00 to −0.45)	<.0001
Baseline absolute volume		−0.001 (−0.008 to 0.005)	.724
Baseline heaviness		−3.48 (−5.85 to −1.12)	.004
Baseline numbness		−2.57 (−5.38 to 0.24)	.073
Presence of fibrosis			
No	74.9% (64.2–85.7)		.299
Yes	68.0% (60.9–75.1)		
History of lymphangitis			
No	74.2% (64.0–84.4)		.343
Yes	67.8% (61.7–73.9)		
Type of surgery			
Mastectomy	68.2% (61.1–75.4)		.567
Quadrantectomy	77.5% (57.9–97.2)		
Lumpectomy	73.5% (56.3–90.7)		
Adjuvant chemotherapy			
No	91.1% (67.9–114.3)		.002
Yes	67.0% (62.2–71.9)		
Radiotherapy			
No	76.8% (61.3–89.0)		.441
Yes	70.4% (63.0–77.9)		
Axillar radiotherapy			
No	81.5% (71.5–91.4)		<.0001
Yes	58.4% (52.2–65.0)		
Dose of radiotherapy		−0.23 (−0.47 to 0.02)	.072
Hormonal therapy			
No	72.4% (60.9–84.0)		.783
Yes	70.4% (62.4–78.4)		

TABLE 2 continued

Factors	ANOVA test (mean; 95% CI)	β coefficient of linear regression (β coefficient; 95% CI)	<i>P</i>
Compliance to bandages			
Good	73.5% (67.4–79.5)		.002
Fair or bad	49.2% (34.5–64.0)		
Number of sessions		–1.17 (–2.59 to 0.25)	.105
Season of treatment			
Winter			
No	76.2% (67.2–85.3)		.056
Yes	62.8% (55.1–70.5)		
Spring			
No	72.2% (64.7–79.7)		.750
Yes	69.8% (56.0–83.5)		
Summer			
No	72.2% (64.5–79.9)		.706
Yes	69.1% (58.0–80.2)		
Autumn			
No	68.7% (61.4–75.9)		.031

*Response was defined as percentage reduction of excess volume
EV excess volume*

TABLE 3 Predictive factors of response after multivariate analysis

Factors	β coefficient of linear regression	<i>P</i>
Compliance to bandages (good vs fair or bad)	β : 25.3 (95% CI: 11.9–38.7)	<.0001
Venous insufficiency in lower limbs (yes vs no)	β : 28.3 (95% CI: 14.9–41.6)	<.0001
Baseline percentage of EV	β : –0.7 (95% CI: –0.9 to –0.4)	<.0001
Season of treatment (autumn vs others)	β : 12.8 (95% CI: 0.9–24.7)	.036

*Response was defined as percentage reduction of excess volume
EV excess volume*

account in this study, it is suggested that an evaluation of the weather conditions during the treatment be added in future studies.

Ramos et al. stated the definition of success in the lymphedema treatment as a reduction in 50% of the excess volume, and they found that the factor that was associated with a good response was not the chronicity of the lymphedema but the volume it had reached.²⁵ They took as a variable the absolute excess volume, without taking into account the relative edema, and they categorized the variable into three levels. The group of patients with less edema showed a better response to decongestive treatment (a mean reduction of 78%), and the patients with more edema showed a worse response (58.9%). The same association was found by our group, in a multicenter study.²⁴

In the current study, we also found that the lower the percentage of excess volume (PEV) was, the more important was the reduction after the treatment. These data support the idea that more severe lymphedema patients have a worse response to treatment. As other authors recommend and our results confirm, decongestive treatment in early stages can bring better results.^{1,17}

The results of our study showed that when the patient suffered a venous insufficiency, the reduction was more important. This can be explained by the fact that a part of this EV was a venous stasis that could drain more easily with decongestive treatment and so give a better result.

Other factors that have been associated with a poor response have been fibrotic consistency, weight increase, a larger weight, and the opposite; weight loss is correlated with a reduction in EV.^{23,24,42} In our study, these variables were not found to be associated with the outcome.

Vignes et al. were the first to study the predictive factors of response to decongestive treatment in a wide prospective cohort of BCRL patients.²⁶ They found that the BMI and the chronicity of lymphedema were predictive factors of response when the response was measured in absolute values of reduction in lymphedema volume. No predictive factors were found to be significant when assessing the relative percentage of edema reduction. They found that a higher BMI was related to a larger absolute reduction of lymphedema volume.²⁶

The association between the chronicity of lymphedema and the response to CDT is not clear: Vignes et al. found

that longer duration of CDT was related to a larger reduction in the absolute lymphedema volume, although some other authors failed to find a significant association.^{22,25,43}

It is very important to underscore that the chronicity of lymphedema has been considered a factor influencing the response to the treatment.²⁶ Lymphedema is a progressive disease, and it has been demonstrated that patients reach higher levels of severity with time and because of the stimulation of fibroblasts, keratinocytes, and adipocytes with the onset of dermal complications as fibrosis, hyperkeratosis, and increased deposition of subcutaneous fat.^{6,44–47} Therefore, the chronicity of the lymphedema before treatment was hypothesized to be associated with a more negative outcome of the therapy, but this is not the case in our study, and patients can benefit from the treatment a long time after the onset of the symptoms. Nevertheless, it must be noted that for 95% of the patients in our group, the duration of lymphedema before treatment was less than 5 years (3.1–5.0). It is not excluded that there is a critical period before the treatment that affects the therapy outcome, and further research is guaranteed because this critical period, if it exists, would be crucial when planning treatments.

In conclusion, it was found that one of the most important predictive factors of the response to CDT is bandage compliance. Therefore, patient motivation and involvement is essential in the treatment. In addition, data support firmly the idea that more severe lymphedemas have a worse response to treatment, and therefore it should be recommended in early stages.

The association between the season of treatment and the response was also very strong. Therefore, an additional factor that must be taken into account in further studies are the weather conditions, such as cold or warm weather or relative humidity that introduced seasonal variations in the data, and comparison of these results in different countries with wider variety of weather conditions is also suggested.

Finally, the results indicate that the chronicity of the lymphedema was not affecting the outcome of the therapy, although in our sample the maximal time before therapy was 5 years.

ACKNOWLEDGMENTS The author would like to acknowledge the excellent work of P. Rel supporting this study.

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