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A Pilot Study to Determine the Extent of Chemotherapy-Induced Polyneuropathy (CIPNP) in Breast Cancer Patients

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Abstract

Introduction: Chemotherapy induced polyneuropathie (CIPNP) is seen in up to 70% of all breast cancer patients (BC). Due to the high number of long-term surviving patients, side effects are becoming increasingly important, especially when they permanently affect quality of life, such as CIPNP. A reduced ability to stand and the associated tendency to fall due to CIPNP is of great importance for patients. First goal of this study was to identify differences in the equilibrium behavior of BC with CIPNP compared to BC patients without CIPN by means of post-urographic measurements. Second goal was to detect a means for the diagnosis of equilibrium disorders to meet the requirements of everyday life.

Methods: A total of 83 patients (pts) participated in the study. 20 of these had developed a CIPNP while, 32 did not (NCIPNP). 31 pts had not received chemotherapy and therefore did not have PNP (NPNP). A clinical examination, focusing on CIPNP, was done. In addition BC had to carry out seven different stand conditions on an AMTI Netforce, which is a force measuring plate. During the test, the parameters centre of pressure (CoP) X Average, centre of pressure (CoP) Y Average, Area and Average Velocity were determined.

Results: Regarding tandem stand with closed eyes, the group with CIPNP had a 17.85 cm^2 larger fluctuation in the mean value difference of the area (fluctuation area) compared to NCIPNP or NPNP ($p=0.04$). Viewing the terminations in the tandem stand with closed eyes, the termination rate in the group with CIPNP was 80%, in NCIPNP 38% and in the NPNP group 61%. ($p<0.001$)

Conclusion: The present study showed that CIPNP in breast cancer pts is underestimated by using simple bipedal or the monopedic standimg to assess the equilibrium of pts. The real impairment of the patients' system of equilibrium with CIPN was evident both in the area of fluctuation (Area) and in the high termination rates, which is important to know regarding everyday life questions like risk of falling or injury.

Keywords: Polyneuropathy; Breast cancer; Post-urographic measurements.

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Introduction

The purpose of this study is to assess the extent of chemotherapy-induced polyneuropathy (CIPN) and their meaning for the stability of the stability of the patients. At about 32%, breast cancer is the most common new cancer among women. Statistically, about every 8th woman suffers from breast cancer in the course of her life [1,2]. For women, the relative five-year survival rate is currently 88% and the relative ten-year survival rate 82% [3]. The taxanes regularly used in breast cancer therapy interrupt the microtubules of the mitotic spindle apparatus and consequently influence not only the axonal transport but also the soma of the sensory neurons. Paclitaxel provides a PNP in 30% of all cases and in combination with platinum analogues even in 70% [4]. Due to the high number of long-term surviving patients, side effects are becoming increasingly important, especially when

they permanently affect quality of life, such as chemotherapy-associated polyneuropathy. A reduced ability to stand and the associated tendency to fall due to CIPNP is of great importance for patients

The diagnosis of a peripheral polyneuropathy and its sociol relevance are fixed on an internal and/or neurological examination [5]. This does not take into account the fact that the degree of PNP is not necessarily congruent with the impairment of the patient in everyday or working life. The most important dimension of PNP for the patient in everyday and working life is probably the disturbance of the sense of balance. This is recorded inadequately in the routine examination [6]. This calls for a new measuring method that enables a more everyday assessment of patients. In the present pilot study, the clinical investigation of equilibrium ability is to be supplemented by post-urographic measurements [7,8].

The aim of the study is to use post-urographic measurements to show differences in the equilibrium behavior of breast cancer patients treated with chemotherapy and the resulting PNP compared to breast cancer patients who have not developed PNP, and at the same time to detect a means of diagnosing equilibrium disorders in order to meet the demands of everyday and professional life.

Materials and Methods

The study involved 100 patients. Inclusion and exclusion criteria are listed in **Table 1**. A survey of the PNP status took place as part of an internal examination in accordance with the guidelines by testing the muscular self reflexes, testing the sensation of vibration and Romberg's stand test.

The study participants were examined in the laboratory of the Sports Science Institute of the Philipps-University Marburg using AMTI Net force plate. It was previously tested in a short one-leg stand on which leg the study participant felt more secure. This decision was relevant during the investigation for both tandem and one-legged stands. At the time of the measurement, the investigator did not know which group (chemotherapy treatment or no chemotherapy treatment) the patient belonged to. Patients had the task of carrying out seven different stand conditions, each lasting 35 seconds. If standing condition was aborted within this time, a retry was granted. With two aborts, the transition to the next standing condition took place. The order and procedure during and between the tests were defined in the study protocol. While pts are located on the force plate, the study participants had eye contact with a point aligned to their respective eye level, which was fixed by magnet on a room-high, grey partition wall and was intended to serve as a fixation object in standing conditions with their eyes open. During the test, hearing protectors were worn to minimize the potentially detrimental effect of noise and loud noises on the balance system [9]. In between the tests, pts were given a break of 30 seconds during which the hearing protectors could be removed and the muscles strained by the stand loosened by walking around or shaking them out.

The first standing was a hip-wide, parallel, bipedal stand with open eyes, followed by a hip-wide, parallel, bipedal stand with closed eyes and finally a hip-wide, parallel, bipedal standing with open eyes and a head placed as far as possible into the neck. The aim of this change in this condition was to deprivate the various components of the equilibrium system. Closing of the eyes minimized the visual component, while the overstretching of the head meant an impairment of the vestibular system. The fourth standing, a so-called tandem stand, was carried out with the eyes open, with the feet arranged so that large toe of the rear foot touched the heel of the front foot and the feet formed a line. The foot that represented the rear foot at the tandem stand was the foot of the leg which was selected as the supporting leg at the beginning of the test. This was followed by a tandem stand with closed eyes **(Figure 1)** and a sixth variation, a tandem stand with open eyes and an overstretched head as far as possible. The final step was a one-leg stand, in which the pts stood on the leg they declared to be their supporting leg and kept the thigh of the other leg as parallel as possible to the floor, while the knee joint flexion to the thigh was 90 degrees. This last standing was only successfully completed after 100 seconds, but did not

Table 1 Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Patients with breast cancer between 18 and 65 years of age	Pre-existing neurological diseases
Chemotherapy not more than six months ago	Known metastases in the peripheral or central nervous system
Surgery and radiotherapy of the mamma not more than six months ago	Lack of consent to the investigation

Figure 1 Tandem stand with closed eyes.

have to be repeated if the study participants fulfilled the stand condition for at least 35 seconds. During the standing conditions, the parameters Centre of Pressure (CoP) X Average, Centre of Pressure (CoP) Y Average, Area and Average Velocity were determined by AMTI Netforce (force plate).

AMTI Netforce and collected parameters

The postural stability was measured in a calm state on a force plate (AMTI Net Force). This plate measures the force components (Fx, Fy, Fz) acting along three orthogonal axes in the Cartesian coordinate system and the corresponding torques (Mx, My and Mz). The x-direction represents the anterior-posterior, the y-direction the medio-lateral and the z-direction the vertical oscillations. The benchmark in post-urography is the Centre of Pressure (CoP). The CoP corresponds to the point at which the resultant of the force movements of the body is projected onto the force plate. The Area parameter is calculated by distributing the CoP data in both medio-lateral and anterior-posterior directions. It is possible to construct an ellipse based on this data that captures a certain percentage of CoP data [10].

For technical reasons, only pts who were able to maintain a stand for a period of 35 seconds and who thus had a data record available for the entire period of the stand could be consulted for the evaluation of a stand. If a test person succeeded in performing a 35s test in the second attempt, this data record was saved with a note stating that the data collected came from the second attempt. Only data from the first experiment were compared in the evaluation, since the comparison of data from the first experiment with data from the second experiment could be superimposed by a possible exercise effect [11]. The data of pts who were unable to perform a standing condition for a period of 35 s in either the first or second attempt were not included in the evaluation. The subject collective was divided into three groups.

I. Chemotherapy and PNP (CIPNP)

II. Chemotherapy without PNP (NCIPNP)

III. No chemotherapy, no PNP. (NPNP)

The evaluation of the data was performed by unifactorial variance analysis. All evaluations were assumed to be significant with a probability of error of less than 5% ($p<0.05$).

Results

The present study included 100 breast cancer patients. Due to measurement errors or lacking data, 17 were subsequently excluded from the study, resulting in a final sample size of 83 women. The patient characteristics are shown in the following **Table 2**.

In the subjects included in this study, the early tumor stages dominated. The majority of the subjects had either tumor stage I or II. Since all subjects were treated according to the guidelines, all 83 subjects underwent surgery. Those 31 subjects who did not receive chemotherapy all also received radiotherapy of the breast. In the group with chemotherapy, 85% of the subjects additionally received mamma radiotherapy.

Three unifactorial variance analyses were performed to detect differences between the groups. Group membership served as an independent variable, age, height and weight as a dependent variable. It was found that there was no significant difference in height and weight between the groups. With regard to the independent variable age, there is a significant difference between the groups. The group "no chemotherapy, no PNP" (NPNP) was in the mean difference 5.302 years older than the group with "chemotherapy, no PNP" (NCIPNP). This difference was highly significant at a level of $p=0.004$ (0.4%).

Subsequently, the different stand conditions were examined by unifactorial variance analysis, in which the group membership represented the independent variable and the parameters CoP X Average, CoP Y Average, Average Velocity and Area of the corresponding stand condition each represented the dependent variable. In the variance analyses of the bipedal levels and the monopedal level, no significant differences could be detected with regard to the parameters mentioned above. Similarly, there were no significant differences between the groups in the tandem stand with open eyes and in the tandem stand with reclined head.

The tandem stand with closed eyes showed a significant difference between the groups with **(Figure 2)** "chemotherapy and PNP"

Table 2 Patient characteristics.

	Chemo and PNP	Chemo no PNP	No Chemo
Number of pts	20	32	31
Median age	50.85 ± 6.17	48.38 ± 7.25	53.68 ± 5.64
Tumor stage			
I	26	24	-
II	21	6	
III	4	1	
IV	1	0	
Therapy			
Resection	52	31	-
Radiation	45	31	
Anti-hormonal therapy	19	17	
Antibody therapy	11	1	

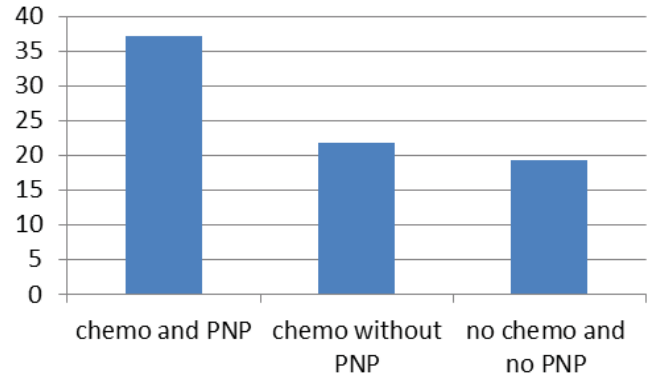

Figure 2 Differences between the three groups in tandem stand with closed eyes. Unifactorial variance analysis with regard to the area in the tandem stand with closed eyes. Independent variable (UV): Groups, dependent variable (AV).

and the group with "no chemotherapy, no PNP", which showed a 17.85 cm^2 larger fluctuation area in the mean difference of the area. This difference was significant at a level of p=0.04 (4%).

Due to the small number of female test subjects who were able to maintain the tandem stand with closed eyes for 35 s and thus influence the evaluation, it seemed relevant to include the termination rate in the evaluation. A unifactorial analysis of variance was performed with group membership as an independent variable and the termination rate in a tandem stand with closed eyes as a dependent variable **(Figure 3)**. All groups differed significantly in the mean difference of the termination rate. These differences were highly significant at a level of p<0.001 (<0.1%).

After considering the drop-out rate, the question arose as to how many female test subjects would succeed in maintaining the tandem stand for 35 s in the second attempt by mobilizing sensorimotor resources with their eyes closed. A unifactorial analysis of variance was carried out with group membership as an independent variable and the percentage increase in the number of women gained as a result of the integration of the second experiment in a tandem stand with closed eyes **(Figure 4)**. All groups differed significantly in the mean difference of the percentage increase in the number of female respondents recruited. These differences were highly significant at a level of p<0.001 (<0.1%).

Discussion

To our knowledge the present study is one of the largest studies to investigate the effect of chemotherapy-induced polyneuropathy in patients with breast cancer by post-urographic measurements of equilibrium behavior. The results of the study show that measurement of the tandem stand with closed eyes seems to have the best potential for discrimination regarding stability uncertainty.

Due to the unique features of the study, it is difficult to embed it in the existing context of studies dealing with oncological patients and post-urography. On one hand, only patients with breast cancer were included in the present study. Comparable studies include different entities of malignancies in their study [12]. On the other hand, the group of volunteers in the present study is sometimes more than twice as large as in the studies [13,14]. The decisive difference, however, is in the composition of the groups, which makes comparison with the other studies more difficult. All studies listed and currently available on chemotherapy, CIPN and balance compare either patients with chemotherapy without CIPN with a healthy control group or patients with CIPN with a healthy control group. In order to exclude a bias by comparison with a healthy control group, it seemed reasonable to us to consider patients with the identical underlying disease but without PNP as a comparison group, since it is unclear to what extent a cancer disease or its psychological and somatic consequences can have an influence on equilibrium behaviour. Only the presence of the two groups "chemotherapy and no PNP" and "no chemotherapy and no PNP" allows a differentiated statement.

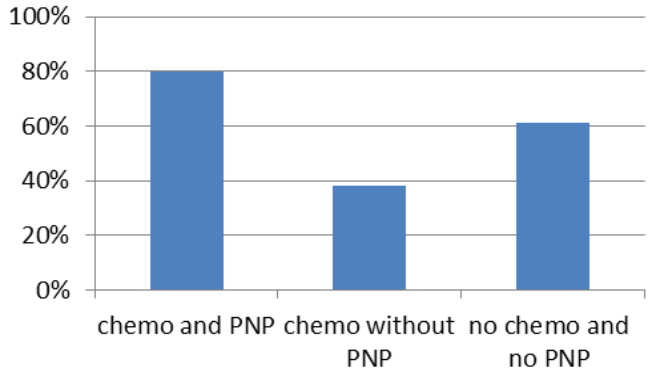

Figure 3 Termination rate in the tandem stand with closed eyes between the three groups. Unifactorial variance analysis with regard to the termination rate in a tandem stand with closed eyes. Independent variable (UV): Groups, dependent variable (AV): Abort rate in tandem stand with closed eyes

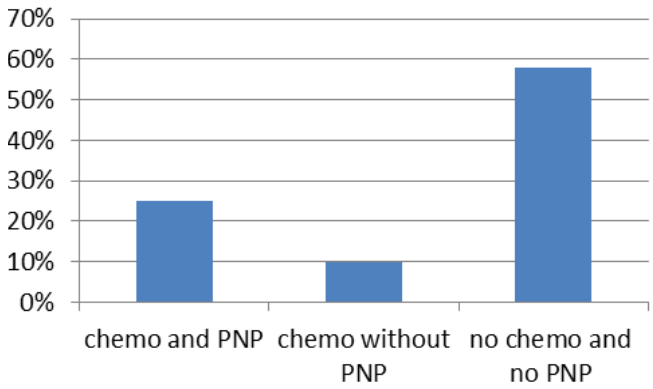

Figure 4 Second try of a tandem stand with closed eyes between the three groups. Unifactorial analysis of variance with regard to the percentage increase of female test subjects gained through the integration of the second experiment in a tandem stand with closed eyes. Independent variable (UV): Groups, dependent variable (AV): Percentage increase of additional female respondents.

When considering the fluctuation in the tandem stand with closed eyes, it was shown that the group with chemotherapy and PNP had a 17.85 cm^2 larger fluctuation area in the mean difference of the area than the group without chemotherapy and without PNP (p=0.04). This result confirms the assumption that the group impaired by chemotherapy and PNP depends to a greater extent on the visual system to maintain equilibrium [15] and varies significantly more due to the deprivation of this major compensation mechanism of their damaged nervous system. Only four volunteers in the group with chemotherapy and PNP were able to maintain the standing condition of the tandem stand with closed eyes for 35s and thus use it for statistical evaluation. For this reason, it is relevant to look at the termination rate of the tandem stand with closed eyes. All groups differed highly significantly (p< 0.01) from each other with regard to the termination rate. The group with chemotherapy and PNP showed by 80% the highest abortion rate as expected. The lowest rate of

abortion with 38% was found in the group with chemotherapy and without PNP.

This result suggests that it is not chemotherapy alone that can negatively influence the ability to balance through its negative side effects such as muscle weakness, anaemia and fatigue, but that the development of PNP as a result of chemotherapy is the decisive factor responsible for high abortion rates in this demanding and relatively unknown state condition. For the authors, this assumption cannot be substantiated by other studies, since no known study with cancer patients or patients with CIPN uses the tandem stand with closed eyes. It is worth mentioning in this context that Schwenk et al., [16], in their study of a sensor-based equilibrium training with cancer patients with CIPN, included the tandem stand with closed eyes in their test planning, but could not take it into account in the evaluation, since the 22 test persons were not able to maintain this stand condition for 30s. The tandem stand with closed eyes was not included in the test planning. This observation confirms how difficult the tandem stand with closed eyes is for patients with CIPN. However, the tandem stand is not only a demanding challenge for the equilibrium system, but also has great relevance in everyday life. When the direction of walking changes, the foot position is naturally changed to a position similar to a tandem position with minimization of the base of support and that in this position the risk of loss of balance is particularly high [17]. This seems particularly relevant for patients with activities on ladders, scaffolds or other difficult standing conditions.

Furthermore, it could be shown that the least affected group with the largest compensation mechanisms experiences the greatest percentage increase in female test subjects through the integration of the second experiment in a tandem stand with closed eyes. The group without chemotherapy and without PNP gained 58% (12 to 19), while the group with chemotherapy and PNP gained 25% (4 to 5). The group, which was neither influenced by chemotherapy nor PNP, seemed to be able to adapt quickly and successfully to demanding requirements of the balance system through better sensory and proprioceptive feedback, which was not possible for the subjects with PNP to this extent.

A similar exercise effect was observed, who had older volunteers train twice a week with a slackline for a period of six weeks under professional guidance [18]. The intervention group was able to significantly increase both its standing time in a one-legged stand and its equilibrium ability in a tandem stand. This experimental set-up with the low-cost and almost ubiquitously usable slack line is also conceivable for measure, as during this twice weekly training over a period of three to four weeks appears to be feasible.

In the overall view of the data, the tandem stand with closed eyes seems to be a suitable instrument for evaluating the ability of patients to respond to a demanding challenge to their balance system i.e., to be a valid instrument for diagnosing a PNP with socio-medical significance.

The present study shows that it is not sufficient to use simple bipedal levels or the monopedal level to assess the equilibrium ability of subjects. The real impairment of the equilibrium system of the test subjects with CIPN can be seen both in the fluctuation area as well as in the high abortion rate and the low rate of female test subjects gained by integrating the second experiment only in the tandem stand with closed eyes. This demanding status, which is largely unknown to the test subjects, enables an assessment of the equilibrium ability in a difficult situation, which is unknown to the test subjects, and could therefore be given increased attention in the clinical examination and in the assessment of the patients. It should be considered to subject patients carrying out activities on scaffolds, ladders or roofs to a post-urographic examination in order to better assess their risk.

In addition, the high rate of female test subjects gained by integrating the second experiment in a tandem stand with closed eyes is a good example of the great exercise effect that exists in post-urographic measurements. This exercise effect was also observed in studies in patients with CIPN [16], so that the provision of targeted medical and physiotherapeutic training programs for this patient group might be useful. 60% of the costs arising from cancer are incurred in the non-medical field and are caused, among other things, by absenteeism and early retirement [19].

Conclusion

Targeted training programmes could possibly counteract this fact. Alternatively, if the data from this study could be confirmed by other studies, it could be discussed whether the tandem stand with closed eyes should be carried out in every examination in order to describe the above-mentioned consequence. Future studies with larger test subject collectives in a tandem stand would have to follow.

Ethics Statement

All patients have given their written informed consent. Study protocol, data collection and analysis procedures, patient information and informed consent were submitted to and approved by the Commission for Ethics in Medical Research of the Philipps-University Marburg (AZ 201/12).

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