Impact of Cancer and 12 Weeks of Chemotherapy on the Balance of the Autonomic Nervous System in Cancer Patients

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ABSTRACT

Cancer and its treatment itself (especially chemotherapy) is associated with number of negative effects on the human body. These include mainly cardiac toxicity, peripheral neuropathy, bone loss, depression, anxiety, nausea, pain, cognitive changes, fatigue, fitness reduction and more. Fatigue is one of the most common negative effects, often persists long after treatment and is described as insurmountable and is associated with lower parasympathetic activity. The autonomic nervous system (ANS) is the main homeostatic regulatory system of the body, it regulates involuntary physiological processes. We believe that this part of the peripheral nervous system can be negatively affected by cancer and chemotherapy, which can have a negative impact on all the processes that control this system. Most drugs used in oncology lead to chemotherapy-induced peripheral neuropathy and are expected to have an influence on the autonomic nervous system. Activity and balance of the autonomic nervous system depend on a range of dynamically changing and quantitatively different conditions such as age, stress, physical activity, sleep, illness, fatigue and more. Methods: To evaluate ANS activity, spectral analysis of heart rate variability (HRV) was assessed. During treatment, 19 oncological patients with prescribed adjuvant chemotherapy measured HRV 3 times a week using a chest strap with a HRV monitor mySASY and mySASY software. Parasympathetic activity (PA), sympathetic activity (S), total score (TS) and total power (TP) were selected as indicators of ANS activity. The patients were women aged 50.38 ± 10,29 with BMI 25,72 ± 4,16. The mean values for the first 14 days of treatment and then for 14 days after 12 weeks of treatment were compared. Data normality was verified by Kolmogorov-Smirnov test (K-S) and static significance was calculated by t-test. All statistical tests were performed at a significance level of 5%. Results: There was a significant decrease in values for three parameters. The PA decreased from 3,80 ± 1,56 to 3,14 ± 1,67 (p = .03), TP decreased from 3,65 ± 1,87 to 2,82 ± 2,08 (p = .04), TS decreased from 3,40 ± 1,67 to 2,67 ± 1,73 (p = .01).

Sympathetic activity was somewhat but not significantly higher, increased from 6,74 ± 1,22 to 6,80 ± 1,44 (p = .83). Conclusion: During the 12 weeks of treatment with adjuvant chemotherapy, there was a significant reduction in parasympathetic activity, total score, and total power. A decrease in PA is usually associated with lower regenerative abilities of the organism, a decrease in TP is associated with a decrease in the activity of the entire ANS. TS evaluates the total power and balance of both ANS branches. The higher the values, the more the body is regenerated and ready for further stress and response to stress.

Keywords: heart rate variability, oncology, neoplasm, tumors

INTRODUCTION

Cancer is a non-communicable disease and is one of the leading causes of death worldwide. There were almost 20 million new cases per year and almost 10 million deaths in 2020 (Ferlay et al., 2020). The most common types of oncological diagnoses are breast, lung, colon and rectal, prostate, skin and stomach cancer (WHO, 2022). Emphasis on primary prevention (early screening) and improvement in the treatment protocols of oncological diseases meant a significant increase in the number of survivors for some types of cancer (Rock et al., 2022). The overall 5-year relative survival rate for all cancers combined in America is now 68 % according to Siegel et al. (2022), although there is noticeable variability across types of cancer.

Cancer and its treatment itself (especially chemotherapy) is associated with number of negative effects on the human body. Chemotherapy side effects and cancer can affect the daily activities of cancer patients and their families on many levels, faced with changes in health status and lifestyle, leading to impaired self-care effectiveness. The most common side effects include cardiac toxicity, peripheral neuropathy, bone loss, depression, anxiety, nausea, pain, cognitive changes, fitness reduction and especially fatigue (Islam et al., 2019; Pearce et al., 2017).

Cancer related fatigue (CRF) is the most common side effect. CFR differs from other types of fatigue in its persistence and severity, often described by patients as unbearable and insurmountable. CRF restricts patients and survivors in daily life (return to work, family life, return to sports and physical activity) and significantly reduces quality of life (Agbejule et al., 2021). According to Fabi et al. (2020) 65% of all patients suffer from CRF, two-thirds of them still suffer from fatigue 6 months after treatment, and almost one-third report fatigue even several years after treatment. The highest incidence is observed in patients who undergo chemotherapy as part of the treatment process (80-90%). The etiology of CFR is not yet precisely described and defined; it is probably a multifactorial process. The influence of the type of tumor, the stage of the disease and the chosen treatment is assumed. In recent years, the influence of inflammation has mainly been investigated. The dependence between the level of inflammatory markers, especially cytokines (IL-1 (interleukin), IL-6, TNFα (tumor necrosis factor alfa)) and the occurrence of CRF is widely investigated (Berger et al., 2015; Bower, 2014). CRF is further associated with autonomic nervous system (ANS) dysregulation. Preliminary data point to the fact that CRF could be associated with lower heart rate variability, specifically with reduced parasympathetic activity(Crosswell et al., 2014; Fagundes et al., 2011; Simó et al., 2018).

The ANS is considered a key system for maintaining homeostasis, its main function is the regulation of the internal environment, ensuring the proper functioning of internal organs, innervation of smooth muscle, blood vessels and glands, and it also affects the activity of the myocardium. Furthermore, the ANS is considered important in regulating the function of the immune system (reciprocal regulation of both systems). This is a very complex process, but in general, higher sympathetic activity is associated with an increase in inflammation and activity of the parasympathetic branch of the ANS with a decrease in inflammation (Crosswell et al., 2014; Irwin & Cole, 2011). Activity and balance of the autonomic nervous system depend on a range of dynamically changing and quantitatively different conditions such as age, stress, physical activity, sleep, illness, fatigue and more. Cancer and chemotherapy have a negative effect on the function of the peripheral nervous system. Most drugs used in chemotherapy cause peripheral neuropathy as a side effect. It can therefore be assumed that these drugs will have a negative effect on the entire peripheral nervous system, which includes the ANS(Adams et al., 2015; Crosswell et al., 2014).

The aim of this work was to evaluate what changes occur at the level of ANS activity during the treatment of an oncological disease and how significant these changes are. The basic premise was the negative effect of cancer and the side effects of its treatment on the human organism. Another goal was to find objective indicators of these changes. These indicators can then be used for further research as monitored parameters for evaluating the effect of various interventions.

METHODS

Participants

The research included 19 participants; the recruitment of participants began in September 2021. All patients were treated at the Masaryk Memorial Cancer Institute. All participants were women with breast cancer aged 50.38 ± 10,29 with BMI 25,72 ± 4,16. Inclusion criteria were set as follows: histologically confirmed diagnosis of malignant tumor with indicated adjuvant chemotherapy based on platinum compounds, taxanes or vinca alkaloids (1), Easter Cooperative Group performance status 0, 1 or 2 (2), the ability to walk 400m without sitting or the help of another person (3) and an estimated survival time of at least 9 months (4). Exclusion criteria were set as follows: inability to perform physical activity (1), terminal stage of an oncological or other disease (2), untreated disease of the lungs, joints or cardiovascular system (3), acute or chronic disease of the immune system or other disease that directly affects this system (e.g. Lupus erythematodes, rheumatoid arthritis, immunosuppressive treatment) (4), pregnancy or breastfeeding (5), current treatment with beta-blockers (6).

Measurement – heart rate variability

HRV spectral analysis was used to assess ANS activity. A chest strap with a mySASY monitor and mySASY software was used to measure HRV. When entering the project, the process of measuring and using the strap and application was explained to each participant. Measurements took place in home conditions 3 times a week; 2x during the working week and 1x on the weekend. Participants were educated to measure themselves in the morning after waking up, without distracting elements (such as talking to someone, watching TV). The measurement itself takes place in the form of an orthostatic test. The first phase takes place lying down, when the monitor reads 120 heartbeats, the next phase is standing, when the monitor reads 360 heartbeats, and the last phase is lying down again and the monitor reads 360 heartbeats again. Parasympathetic Activity (PA), Sympathetic Activity (S), Total Score (TS) and Total Power (TP) were selected as indicators of ANS activity and balance.

Statistical analysis

The basic hypothesis was that chemotherapy has a negative effect on the activity and balance of the ANS. Basic parameters - PA, S, TS and TP were selected from HRV measurements. For evaluation mean values (M) and standard deviations (SD) were calculated for the first 14 days of measurement and subsequently for 14 days after 12 weeks of chemotherapy. The normality of the data was assessed according to the Kolmogorov-Smirnov test (K-S test), which confirmed that the data came from a normal distribution. All statistical tests were performed at the 5% significance level. Statistical significance for individual parameters was tested using a t-test.

Results

Table 1 shows mean values and standard deviations for key parameters in study. The values for the 1st period (the first 14 days of measurement) and for the second period (14 days after 12 weeks of chemotherapy) are shown here. For S there was a slight increase in the value from 6.746 ± 1.223 to 6.804 ± 1.444. However, the increase was not statistically significant (p = .838). There was a statistically significant decrease in values for other three parameters. The PA decreased from 3.804 ± 1.563 to 3.139 ± 1.674 (p = .032), TP decreased from 3.653 ± 1.872 to 2.824 ± 2.088 (p = .045), TS decreased from 3.402 ± 1.669 to 2.675 ± 1.731 (p = .012).

Table 1: Means of key study variables for first and second period of measurment

Variable	**1st period (n=19) (M ± SD)**	**2nd period (n=19) (M ± SD)**	***p* value**[a]
Symphatetic Activity	6.746 ± 1.223	6.804 ± 1.444	.838
Parasymphatetic Activity	3.804 ± 1.563	3.139 ± 1.674	.032*
Total Power	3.653 ± 1.872	2.824 ± 2.088	.045*
Total Score	3.402 ± 1.669	2.675 ± 1.731	.012*

a comparison between periods was tested with t-test

* p < 0,05

M mean value

SD standard deviation

DISCUSSION

Data from previous research assume a negative effect of chemotherapy on the balance of the autonomic nervous system(Adams et al., 2015; Crosswell et al., 2014). Cakan et al. (2022) proved in their study that chemotherapy has a negative effect on HRV in children with cancer, but according to their results, it seems that this change is not permanent or long-lasting in children. Parasympathetic activity (vagal activity) is most often investigated. According to the mySASY manual, the value of parasympathetic activity can range from -5 to 5. The higher the value of parasympathetic activity, the better the organism is regenerated and capable of handling further stress. According to the results, this value decreased from 3.804 ± 1.563 to 3.139 ± 1.674 due to ongoing chemotherapy. In oncology patients, a lower value is associated with a higher risk of cardiovascular complications and higher cardiovascular mortality(Caro-Morán et al., 2016; Vanderlei et al., 2009). Some drugs used for chemotherapy (anthracyclines, cisplatin, taxanes) are expected to have a negative effect on autonomic cardiac regulation. However, it is not yet completely clear whether this is a direct toxic effect on the cells or a negative effect via the vagus nerve (Adams et al., 2015; Simó et al., 2018). Conversely, higher vagal activity is associated with a longer estimated survival time (Zhou et al., 2016). Therefore, a number of studies are devoted to investigating different types of interventions for cancer patients and survivors. Controlled physical activity, mindfulness-based interventions and breathing exercises appear to be effective and have a positive effect on parasympathetic activity (Laborde et al., 2022; Lavín-Pérez et al., 2021; Niederer et al., 2013; Wang et al., 2022).

Sympathetic activity can take on the same values as parasympathetic activity, but here, on the contrary, the lower the value, the better the organism is able to withstand stress (greater system capacity). According to the results, there was an increase in sympathetic values from 6,746 ± 1,223 to 6,804 ± 1,444, but the increase was not statistically significant. In general, sympathetic activity increases when the organism is exposed to a stressor. Stress, which is undoubtedly associated with oncological diagnosis and treatment, leads to an influence on the hypothalamus, the main autoregulatory center, the release of adenocorticotropic hormone and subsequently cortisol, which results in an increase in sympathetic activity and its effect on the regulation of inflammation (Cooper et al., 2015). Total power is a parameter that points to the overall performance of the ANS, it does not differentiate the activity into individual branches. TP can also take values from -5 to 5. The lower the TP value, the lower the activity of the entire system. In the study, TP decreased from 3,653 ± 1,872 to 2,824 ± 2,088 during chemotherapy. Low HRV is associated with shorter survival time in cancer patients (Zhou et al., 2016). Lower HRV is also more common in advanced stages of cancer (De Couck & Gidron, 2013). TS is a complex indicator that, in addition to overall performance, also includes the balance between the branches of the ANS (vagal activity and sympathetic activity). The higher the value, the better the regeneration and the ability to deal with stress. TS decreased from 3.402 ± 1.669 to 2.675 ± 1.731, in terms of statistical significance, this was the largest change of all parameters.

HRV is a very variable indicator that can be influenced easily. Therefore, in the study, it was chosen to use the average of 14 days of measurement to eliminate distortion of the results as much as possible. HRV is influenced by age, stress, quality of sleep and general fatigue, alcohol intake, physical activity and by the state of health of the organism (acute and chronic diseases and their treatment). It was also important to inform participants about the correct measurement methodology and to tried to ensure that they are measured immediately in the morning. However, the measurement took place in home conditions, and it is therefore not possible to directly supervise each participant.

CONCLUSION

In conclusion, during the 12 weeks of ongoing chemotherapy, there were significant changes in HRV parameters. There was a decrease in PA, TS and TP in contrast to an increase in the value of sympathetic activity, which was, however, not statistically significant. For further research, it would be better to have more participants and a wider range of diagnoses. Only women with breast cancer participated in this research, although this was not limited by the inclusion criteria. It would also be interesting to find out whether the decrease in HRV is permanent or long-lasting even after the end of oncological treatment, or whether it will spontaneously return to the original values. Current knowledge shows us that the change is likely to be long-lasting and the goal is to find a suitable intervention for these patients that would help them return to normal family and working life. It is therefore important to choose the right intervention, so that it has a positive benefit not only for HRV values, but also for the overall health of the patient. Above all, the implementation of the given intervention in practice and its availability for patients are essential.

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