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NEUROLOGICAL SIDE-EFFECTS OF CHEMOTHERAPY IN ONCOLOGY, THEIR DEPENDENCE FROM CANCER PROGNOSIS SEVERITY, BMI, GENDER AND CHEMOTHERAPY REGIMEN, POSSIBILITY TO REDUCE SIDE-EFFECTS

Diploma Thesis

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LIST OF ABBREVIATIONS

ASCO	American Society of Clinical Oncology
ANS	Autonomic nervous system
B1	Thiamine
B6	Pyridoxine
B12	Cobalamin
BMI	Body Mass Index
CE	Coasting Effect
CINV	Chemotherapy-induced Nausea and Vomiting
CIPN	Chemotherapy Induced Peripheral Neuropathy
CNS	Central Nervous System
CR	Complete Response
DRG	Dorsal Root Ganglion
DNA	Deoxyribonucleic Acid
DTR	Deep Tendon Reflex
ED_{50}	Effective dose in 50% of a population
EMG	Electromyogram
EORTC	European Organization for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FACT	Functional Assessment of Cancer Neurotoxicity scale
FDA	The US Food and Drug Administration
GPx	Glutathione Peroxidases
HbA1c	Glycohemoglobin
HDI	Human Development Index
HIV	Human Immunodeficiency Virus
IV	Intravenous
LA-12	Cyanocobalamin
LD_{50}	Lethal dose in 50% of a population
MASCC	Multinational Association of Supportive Care in Cancer
MEC	Minimum Effective concentration
MTC	Minimum Toxic concentration
MTSA	Microtubule Stabilizing Agent
NACT	Neoadjuvant Chemotherapy
NCCN	National Comprehensive Cancer Network

NCS	Nerve Conduction Studies
NTIDs	Narrow Therapeutic Index Drugs
OC	Oral Chemotherapy agent
PN	Peripheral Neuropathy
PNS	Peripheral Nervous System
QoL	Quality of Life
TCAs	Tricyclic Antidepressants
TI	Therapeutic Index
USD	United States Dollars
VCR	Vincristine

ABSTRACT

Title: Neurological side-effects of chemotherapy in Oncology, their dependence from cancer prognosis severity, BMI, gender and chemotherapy regimen, possibility to reduce side effects.

Background: Neurological side-effects are a common and severe complication of chemotherapy. They can lead to permanent damage of parts in the nervous system and potentially cessation of chemotherapy. They are often under looked as other side-effects are easily recognizable.
Early intervention could diminish neurological side effects and it could help to fully accomplish chemotherapy and treat cancer better.

Objective: The objective is to:
Find whether cancer patients survival, BMI, gender or chemotherapy regimen have correlation with incidence and severity of neurological side-effects in chemotherapy.
To try to find possibility to prevent chemotherapy side-effects.
To identify which patient group should need more help to reduce side effect symptoms and at the same time not to over-use medicines (money) where it is not necessary.

Materials and methods: The study tool is questionnaire and patient case history based. Patients were selected by stratified random sampling in P. Stradins Clinical University Hospital Oncology department. Patients were all receiving exclusively chemotherapy, surgery and radiation therapy was an excluding factor. Patients reported the neurological side-effects they were experiencing in the questionnaire. Patients in weaker state were interviewed. 200 patients in total were considered for the research and after exclusion 51 patients were included in the study. From the patients 58,9% (n=30) are male and 41.1% (n=21) are female. From the patients 70.6% (n=36) were receiving platinum based chemotherapy and 29.4% (n=15) were receiving non-platinum based chemotherapy.
The cancers that have a better prognosis (one-year survival >70%) were breast (n=6), prostate (n=4), testicular cancer (n=4) and melanoma (n=1). The cancers with worse prognosis (one-year survival < 70%) were lung (n=13), colorectal (n=13), urothelial (n=1), ovarian (n=2) and pancreatic cancer (n=4), and non-Hodgkin's lymphoma (n=3).

Results: Regarding the prognosis of cancer and the number of neurological symptoms (p value) < 0.05. Therefore, patients with a 1-year cancer prognosis <70%, have significantly higher

number of neurological symptoms (mean number 1,60) compared to those that have a better prognosis (mean number 2,81).

In the prognosis patient groups, for presence of Headache (p value) = 0.05 and for autonomic nervous system induced freezing (p value) < 0.05, which indicates that patients with worse prognosis, have significantly higher presence of headache and freezing.

For Headache intensity in prognosis groups (p value) < 0.05 which indicates that patients with a 1-year cancer prognosis <70%, have significant higher intensity of headache.

For ANS induced sweating in the prognosis groups, (p value) > 0.05 which indicates that for this sample size no significant difference is observed. However, p value is close to 0.05 therefore a larger sample size is possible to indicate statistically significant differences.

Conclusion: Cancers with 1-year survival prognosis <70% have significantly more neurological side-effects.

Number of patients with headache and higher headache intensity is larger in worse survival prognosis group.

BMI and gender did not correlate in statistical significance with incidence and intensity of neurological side-effects.

We can use these results in daily practice of Oncological chemotherapy, by preventively prescribing analgesics for shorter survival prognosis patients group.

We could prescribe more autonomic nervous system stabilizers (e.g. Fenibut) for patients with serious freezing in patient group with low life expectancy, improving their quality of life.

There is no need, according our results, to implement these measures in patients with a longer life expectancy, or according to gender and BMI.

Timely prevention of side effect symptoms from one side, possible minimizing of not-needed pharmaceuticals from the other side, could diminish patient suffering and make a positive economic impact to cancer management.

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Key words: Chemotherapy induced peripheral neurotoxicity (CIPN), Chemotherapy induced nausea and vomiting (CINV), Autonomic nervous system (ANS), Platinum chemotherapy, Body mass index (BMI), Quality of life (QoL).

KOPSAVILKUMS

Virsrakst: Onkoloģiskās ķīmijterapijas izraisītas neiroloģiskās blakusparādības, to atkarība no pacienta dzīvildzes prognostiskajiem rādītājiem, ĶMI, dzimuma un ķīmijterapijas veida, iespēja blaknes mazināt.

Priekšvēsture: Neiroloģiskās blakusparādības ir samērā biežas un nopietnas ķīmijterapijas blaknes. Ķīmijterapija var izraisīt pastāvīgus nopietnus bojājumus nervu sistēmā, ko reizumis nākas novērst, pārtraucot ķīmijterapiju. Neiroloģiskās blaknes bieži paliek neievērotas, atšķirībā no citām vieglāk pamanāmām. Agrīna iejaukšanās varētu mazināt neiroloģiskās blaknes, tas palīdzētu veikt pilnvērtīgu ķīmijterapijas kursu un labāk ārstēt vēzi.

Mērķis: Mērķis ir noskaidrot, vai vēža pacienta paredzamā dzīvildze, ķermeņa masas indekss (ĶMI), un dzimums korelē ar izraisīto neiroloģisko parādību biežumu un smagumu.
Mēģināt rast iespēju profilaktiski mazināt neiroloģiskās blaknes.
Ja kaut kas no minētā apstiprinātos- vai iespējams paredzēt, kurai pacientu grupai vajag un var vairāk palīdzēt mazināt blakņu simptomus, vienlaikus nevajadzīgi nepārtērējot medikamentus (naudu) pacientiem, kam tas nav īpaši nepieciešams.

Materiāli un metodes: Pētījums ir balstīts aptaujas anketās un pacientu vēsturu materiālos.
Pacienti tika izvēlēti, nejauši atlasot tos P. Stradiņa Klīniskās Universitātes slimnīcas Onkoloģijas nodaļā. Izvēlēti tika pacienti, kas saņēma tikai ķīmijterapiju. Izslēdzošie faktori bija saņemta ķirurģiska ārstēšana un vai staru terapija.
Pacienti anketā rakstiski ziņoja neiroloģisko blakusefektus ar kuriem tie saskaras. Pacienti sliktā stāvoklī tika intervēti.
Kopumā 200 pacientu materiāli tika izvērtēti un pēc atlases un izslēgšanas 51 pacients tika iekļauts pētījumā.
No tiem 58,9% (n = 30) ir vīrieši un 41,1% (n = 21) ir sieviete. No pacientiem 70,6% (n = 36) saņēma platīnu saturošu ķīmijterapiju un 29,4% (n = 15) saņēma mazāk toksisku ķīmijterapiju (neplatīna).
Vēži, kurām bija labāka prognoze (viena gadu dzīvildze> 70%) bija krūts (n = 6), priekšdziedzera (n = 4), sēklinieku vēzis (n = 4) un melanoma (n = 1). Vēži ar sliktāku prognozi (viena gadu dzīvildze <70%) bija plaušu (n = 13), resnās un taisnās zarnas (n = 13), uroteliālais (n = 1), olnīcu (n = 2) un aizkuņģa dziedzera vēzis (n = 4) un ne-Hodžkina limfoma (n = 3).

Rezultāti: Vēža dzīvildzes prognoze un neiroloģiskie simptomi (p vērtība <0,05).

Pacientiem ar 1 gada vēža prognozi< 70% ir ievērojami vairāk neiroloģisko simptomu (vidējais skaits 2,81), salīdzinot ar tiem, kam ir labāka prognoze (vidējais skaits 1,60).

Pacientu grupā ar sliktāku prognozi galvassāpes (p vērtība = 0,05) un veģetatīvās nervu sistēmas izraisīta salšana (p vērtība <0,05) norāda, ka pacientiem ar sliktāku prognozi tās ir ievērojami biežākas.

Galvassāpju intensitāte sliktākas prognozes grupā (p vērtība <0,05) norāda, ka pacientiem ar 1 gadu vēža prognozi < 70% ir ievērojama lielākas intensitātes galvassāpes.

VNS/ANS izraisīta svīšana abās grupās (p vērtība> 0.05) norāda, ka netiek novērota nekāda būtiska atšķirība. Tomēr p vērtība ir tuvu 0,05 tādēļ, iespējams, ar lielāku pacientu skaitu parādītos statistiski nozīmīgas atšķirības.

Secinājumi: Vēža prognozes smagums, paredzamā dzīvildze korelē ar neiroloģisko blakusparādību biežumu, kas ir lielāks sliktākas prognozes grupā.

Pacientu skaits ar sliktāku izdzīvošanas prognozi, kam bija galvassāpes, lielāka galvassāpju intensitāte un autonomās nervu sistēmas radīta salšana, svīšana, arī ir lielāks, nekā grupā ar vēža 1 gada izdzīvošanas prognozi> 70%.

Pacientu ĶMI, dzimums un zāļu veids nav statistiski ticami saistāms ar neiroloģisku blakusparādību biežumu vai izteiktību.

Mēs varam izmantot šos rezultātus ikdienas onkoloģiskās ķīmijterapijas praksē, nozīmējot analgētiskos līdzekļus laikus, pacientiem kam tas nepieciešams.

Mēs varētu nozīmēt vairāk autonomo nervu sistēmu stabilizējošus līdzekļus pacientiem ar izteiktu salšanu (sliktākas prognozes grupā), uzlabojot viņu dzīve kvalitāti.

Pēc mūsu pētījuma rezultātiem, tas nebūtu jādara pacientu grupai ar labāku izdzīvošanas prognozi, kāda īpaša dzimuma vai ĶMI pacientiem.

Laicīga ķīmijterapijas blakņu novēršana, nevajadzīgu zāļu nenozīmēšana kopumā mazinātu pacientu ciešanas un dotu pozitīvu ekonomisko efektu.

Protams pirms pasākumu ieviešanas šis pētījums būtu jāveic ar ievērojami lielāku pacientu skaitu.

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Atslēgvārdi: Ķīmijterapija izraisīta perifērisko neiropātija (ĶIPN), ķīmijterapijas izraisīta slikta dūša un vemšana (ĶISDuVa), veģetatīvo/autonomā nervu sistēmu (VNS), platīna ķīmijterapija, ķermeņa masas indekss (ĶMI).

1. Introduction

Cancer affects people all around the world independent of age, race and development of countries. In 2012, there were 14.1 million new cancer cases in the world and 8.2 million cancer related deaths. It is currently estimated that the incidence of new cancer cases will rise to 23.6 million by the year 2030. More than 40% of cancer cases are in countries with low or medium Human Development Index (HDI). The highest incidences are in the United States of America and Australia, both with over 300 new cases per 100,000 people. The four most common cancer types are prostate, female breast, bowel and lung cancer which is strongly associated with cigarette smoking. Lung cancer is the most common cancer in men and accounts for more than 1 in 10 of all cancer diagnosed. It is evident that the incidence of cancer is rising and there is a major demand of antineoplastic therapy in the future as well. (Cancer research UK, 2016)

In 2015, the global cancer treatment grew to 107 billion United States Dollars (USD). The oncology drug market is projected to grow 7.5 – 10.0 % annually until 2020 when the market reaches 150 billion USD. The oncology market is fueled by constant innovations and the goal for making more efficient and less toxic drugs. (Tor Constantino, 2015)
There are several ways to approaches to cancer treatment: chemotherapy, radiotherapy, immunotherapy, surgery and ablative procedures. This research focuses on chemotherapy from these modules. It has been known for decades that antineoplastic drugs are toxic and along with cancerous cells they kill healthy cells as well. Chemotherapy aims to damage abnormal cells as they divide, to control the spread and growth of cancer, however, normal cells can replace or repair healthy cells that have been damaged by chemotherapy. For this reason, many side-effects caused by chemotherapy are reversible.

The use of antineoplastic agents has increased greatly over the last decades. Survival rates post cancer have increased and patients' quality of life plays a more important role than it did in the past when survival rates were lower. Now the 5-year cancer survival rate is 66% and the amount of cancer survivors rising. The complications and side-effects related to cancer are a growing concern since many drugs have a high toxicity profile. Neurological side-effects happen frequently and may potentially be the reason to limit the dose of chemotherapy or discontinue treatment. Bone marrow suppression is one of the most common side-effects but it can be overcome by growth factors or bone marrow transplantations. Chemotherapy may cause both peripheral and central neurotoxicity. The peripheral toxicity manifests as peripheral neuropathy

with loss of sensation and weakness. The central neurotoxicity manifests as nausea and vomiting, dementia, minor cognitive deficits and in the worst cases coma.

Management of neurological symptoms is mainly reducing the cumulative dose of the chemotherapeutic agent or reducing dose intensity. Cessation of treatment may be necessary if symptoms are severe and threaten the health of the patient. Neuroprotective agents have been introduced but the evidence is limited and beneficial results have only been observed with certain drugs. (Verstappen, 2003)

Currently there is demand to research adverse effects of chemotherapy and to develop new methods to counteract them. There are several factors that determine how probable neurological side-effects may be. Platinum containing drugs are known to be neurotoxic and in this research, we will also compare platinum containing to non-platinum drug therapies. Frequently drugs are given in combinations and this proposes a challenge in identifying which drug is the most neurotoxic when given as a combination.

1.1 Objective

The aim of the study is:

- To analyze whether severity and prognosis of cancer correlates with neurological side-effects.

- To identify incidence and significance of neurological complications in two groups: platinum and non-platinum receiving groups.

- To analyze whether BMI has correlation with neurological side-effects in chemotherapy.

1.2 Tasks

- To compare whether prognosis / severity of cancer have an impact in neurological side-effects.

- To compare neurological side-effects of platinum and non-platinum chemotherapy receiving groups by several different neurological parameters.

- To compare whether BMI (<=25, > 25) has an influence in incidence or severity of neurological side-effects.

- To compare if gender is an influencing factor in incidence or severity of neurological side-effects.

2. Literature review

2.1 Chemotherapy, General principles

The goal in cancer treatment is primarily elimination of cancer. Incase this cannot be accomplished; the aim is set for palliative care including management of symptoms and striving for quality of life and extending life. With new advances in cancer treatment the combined 5-year survival time of all cancer patients is 66%. For this reason, there are more than 13.7 million cancer survivors in the United States alone. This amount is increasing by 2% annually. (Travis, 2014)

Cancer treatment comes with side-effects that may question the beneficence; not to do more harm than good for the patient. For instance, every cancer treatment has the possibility of causing harm, and in the worst case produces toxicity and no benefit at all. In chemotherapy treatment, the therapeutic index may be quite narrow and the drug is given to the point of toxicity. On the other hand, in palliative care the focus is more on decreasing and minimizing the effects of drug toxicity.

The therapy for cancer treatment is generally divided in to two main groups: local and systemic treatment. The content of this paper focuses on the systemic treatment modality, chemotherapy. This can be molecularly targeted or hormonal therapy. The third variant being biological therapy which includes immunotherapy. Chemotherapy is frequently given as a combination treatment and agents in one group can act by different mechanisms. Radiation therapy, surgery and ablative procedures conclude the local treatment regimens. Radiofrequency and cryosurgical approaches are included in the ablative procedures.

For older population cancer incidence is higher than for younger population. Therefore, the current epidemiologic development suggests that the overall incidence of cancer in the Western world is increasing in all cancer cases. Despite knowledge of this fact, the very old population is underrepresented in cancer clinical research and being over the age of 70 is often an exclusion criterion. There is widespread critique regarding this issue, but new exclusion criteria have not yet been implemented. The very old population is often weaker and do not tolerate the treatment as well. They also tend to have more comorbidities which affect the overall prognosis of treatment. Fear of increased toxicity and uncertainty of clinical value may affect the decisions made by oncologists for cancer treatment in older population. However, according to a new

study higher age did not significantly affect the survival rates of patients. (Berger et al, 2015) (Goto, 2012)

2.1.1 Oral chemotherapy

More than 25% of the 400 neoplastic drugs in development are oral chemotherapy agents (OC) and the number of OC available have significantly increased over the last decade. OC agents pose many of the same risks as intra venous (IV) agents despite the route of administration. OC may pose an even higher risk of drug-to-drug interactions due to absorption and metabolism. Similar strict protocols do not usually exist for OC agents as they do for IV agents. As a lack of standardization of OC, American Society of Clinical Oncology (ASCO) produced new safety guidelines in 2013 which specifically included OC. The benefits of OC are that the therapy can be performed in an outpatient setting and that venous access points are not needed. The setback is that the drug doses cannot be monitored and more responsibility of treatment is placed on the pharmacists. (Shav, 2016)

2.1.2 Venous and arterial chemotherapy

At this time, there are two approaches for vascular infusion chemotherapy, intravenous systematic chemotherapy and intra-arterial interventional chemotherapy. The benefit of intravenous chemotherapy is the lower equipment requirements but the drawback is that it is assumed to cause heavier systematic side-effects. Intra-arterial chemotherapy is more expensive and is more challenging for technicians to administer. For example, in treatment of ovarian cancer there are promising results with higher drug concentrations in the pelvic cavity and enhanced killing of tumor cells by 10-100 times. However, in several studies the efficacy and clinical outcome were similar with both approaches. The administration of neoadjuvant chemotherapy (NACT) is done in cycles, followed by an appropriate recovery time. The number of cycles varies depending on the cancer and drugs in question. If surgery is planned for treatment also, patients fitness and age play an important role in assessing the eligibility for this option. Neoadjuvant chemotherapy is defined as a first step to try and shrink a tumor before the main treatment, which is usually surgery. Similarly, induction chemotherapy is defined as the use of chemotherapy as an initial treatment prior to surgery or radiation therapy. (Ting, 2014)

2.1.3 Cancer chemotherapy, therapeutic index

The therapeutic index is the amount of separation amidst toxic and therapeutic doses. In other words, it can be explained by a ratio that compares the concentration of a drug in blood circulation to cause a therapeutic effect to the amount that causes toxicity. In animal trials, it may be compared to the amount that causes death instead of toxicity. Most useful drugs have large therapeutic windows. The unfortunate property of current chemotherapy is that targets are present both in normal tissue and cancer tissue, making the therapeutic indices moderately narrow. Therapeutic index (TI) can be calculated by dividing lethal dose of a drug in 50% in a population (LD_{50}) by the effective dose in 50% in a population (ED_{50}). $TI = LD_{50} / ED_{50}$. There are volatile interpretations of TI in academic settings depending on which toxic effect is under investigation. This directly affects the definition used in each case separately. In practice TI used is the range of doses that give high enough effectiveness without unacceptable adverse effects. Fortunately for most drugs the range is wide enough and doses are well above minimum therapeutic concentration and adequately below the concentration that will induce toxicity. With this in mind it, can be expected that drugs prescribed will have the required safety margin and have clinical efficacy for the patient.

The range between ED_{50} and TD_{50} can be extensive depending on the medication used. A drug that has a wide TI is considered safer because it is easier to use and more difficult to overdose. On the contrary, a drug with a narrow TI is more likely to cause side-effects because it has an abrupt concentration-response relationship with toxicity and efficacy. When TI exceeds the value of 10 it is generally considered a good safety profile. Narrow TI drugs (NTIDs) have a very different profile. There is a very narrow spectrum in which the drug will cause a therapeutic effect without toxic or possibly fatal consequences. Small plasma concentration changes may result in an inadequate therapeutic response and induce unwanted toxic side-effects. NTIDs are often called “critical dose drugs” because the relatively small differences in concentration can lead to serious drug reactions and failures of therapy.

The FDA (the US Food and Drug Administration) has a definition for NTI which includes three different parts. (a) Median lethal dose LD_{50} and medial effective dose ED_{50} have less than a twofold difference, or (b) Minimum toxic concentration (MTC) and minimum effective concentration (MEC) in blood have less than a twofold difference between them and (c) the administration and use of the drug requires patient monitoring and careful titration.

It should be considered that the use of NTIDs must be individualized because small changes in dosage can considerably change the pharmacological response. Patients receiving multiple medications, have comorbidities or have advanced age particularly are at risk for sub therapeutic or toxic effects.

In clinical medicine the NTI is important for proper use of drugs. It is used by clinicians in the sense that there is practical knowledge of drug doses and plasma concentrations that induce the therapeutic effect versus toxic side-effects. In this way clinicians can evaluate the best possible drug to cause the desired effect and diminish toxicity as far as possible. (Tamargo, 2015)

2.6 Platinum containing drugs

Cisplatin was the first platinum containing antineoplastic drug and was adopted for use in 1970. It was developed in mid-60s and more than 3000 platinum compounds have been developed since then. 35 of these compounds have exhibited adequate pharmacological advantages and have been in clinical use. Second generation drugs like carboplatin, nedaplatin, tetraplatin, iproplatin and third generation oxaliplatin, lobaplatin, heptaplatin, satraplatin and LA-12 have clinically a better safety profile.

Platinum containing drugs have earned their place in routine cancer treatment. Their toxicity features vary from other compounds and the platinum induced peripheral neuropathy (PN) is a common feature. (Pabla, 2012)

The main target of platinum compound-induced damage is the dorsal root ganglion (DRG) and there is a direct correlation between the platinum levels is DRG and the severity of PN. The early PN manifestations include decreased vibratory sensitivity in the toes and loss of ankle jerks. Other symptoms being numbness, tingling or paresthesia of fingers and toes. The paresthesia typically starts at the edges of fingers and toes and spreads inwards. Prolonged use tends to affect the deep tendon reflexes (DTR) and the loss of more proximal vibratory sense. Platinum drugs tend to affect temperature and pin sensation less, as well as joint position perception. However, the sensation of body in space is impaired. In the more severe clinical cases platinum containing therapy may affect proprioception and result in an ataxic gait.

The PN induced by oxaliplatin results in two different types of clinical syndromes; acute and chronic. The acute is characterized by transient paresthesia in the distal extremities and early onset perioral paresthesia. The chronic is a cumulative sensory neuropathy with the classical platinum drug PN. The symptoms are worsened by cold.

Platinum drug induced PN usually starts during chemotherapy but may progress 2-6 months after cessation of chemotherapy knows as the coasting effect. This occurs in up to 30% of cisplatin receiving patients. The cumulative dose given is the main risk factor of receiving persistence of neurotoxicity. PN induced by oxaliplatin is more reversible and completely resolves in about 40% of patients in 7 months after discontinuation of the drug, however, coasting effects may also occur.

Platinum induced PN is closely related to the accumulated dose and the dose intensity given. It is expected for cisplatin induced PN to appear after a dose of 250-350 mg/m2 or a cumulative dose of 500-600 mg/m2. Almost all patients get objective neurological symptoms with these doses and at least 10% are severely impaired.

PN associated with carboplatin is less frequent and severe when compared to cisplatin with conventional doses. (Lee et al, 2012)

2.6.1 Cisplatin

Cisplatin was the first heavy metal used in various cancers, particularly in lung, ovary and cancers of testis. Most patients developed a symptomatic neuropathy and second generation platinum drugs were developed for this reason. From the second-generation drugs carboplatin could be used for the same indications and symptomatic neuropathy was considerably reduced. In a recent Cochrane review, first and second generation platinum drugs were combined with third generation drugs for treatment of advanced non-small cell lung cancer. The incidence of neurotoxicity went up by two-fold in the carboplatin group. Oxaliplatin from the third generation of platinum drugs was developed for metastatic colon cancer has a 70% rate of neurotoxicity according to the Food and Drug Admististration (FDA) and often leads to treatment discontinuation. In other studies, neurotoxicity rates of up to 80% have been reported with oxaliplatin.

Platinum containing drugs are almost always given in combination with other chemotherapy drugs or radiation therapy which may be neurotoxic on its own. Ototoxicity is another side-effect of platinum drugs and is progressive and irreversible. It usually presents bilaterally and can occur after years of treatment. Cisplatin is believed to be the most ototoxic and oxaliplatin the least. The mechanism of action is based on the accumulation of cisplatin in the cochlear tissue. DNA adducts are formed along with dysfunctional protein and enzyme synthesis leading to apoptosis of auditory sensory cells. (Abolfazl et al, 2014)

It is believed that cisplatin has an effect in the central nervous system (CNS) causing headaches, especially seen in patients that did not previously have any forms of headaches. The headache in general in worse in the mornings and exacerbated by coughing and straining. It is described as generalized, constant pressure and medium intensity. (Clarke, 2016)

2.7 Vinca Alkaloids

The vinca alkaloid group of chemotherapeutic agents include both natural alkaloids and semi-synthetic compounds. Of the natural alkaloids vincristine and vinblastine are commonly used and from the semi-synthetics drugs vindesine and vinorelbine are the most common. This group of drugs has a broad spectrum of indications for use. Indications are hematological and lymphatic malignancies as well as solid tumors such as breast, ovaries, testicular, brain, non-small cell lung tumors and sarcomas. Vincristine is the most neurotoxic from vinca alkaloids.
PN induced by vincristine typically manifests as the loss/decrease of DTN and paresthesia. In prolonged use, muscular weakness can occur in extensor muscles, especially of ankles and toes. Muscle cramps are typical in high-intensity treatment. Joint position sense and vibration sense are usually not affected. Objective touch and two-point discrimination sensory loss is usually mild and limited to fingers and toes. Pain can be observed in some cases mainly in the skin of fingers and toes with an increase of warm and sharp detection threshold. (Argyriou et al, 2012)

2.7.1 Vincristine

Vincristine (VCR) is one of the oldest antineoplastic drugs. Still the incidence of PN is unknown due to heterogeneity of chemotherapeutic regimens in different types of tumors.
As with cisplatin, PN related with vincristine is dose related. When the patient is receiving at least 4mg/m2, loss or decrease of DTR in ankles is observed. Dose of 2-6 mg/m2 is reported to cause distal paresthesia. Total dose of 8 mg/m2 can cause development of motor weakness or gait impairment. Vincristine PN is usually reversible but muscle weakness and paresthesia can persist for 3 months after discontinuation of treatment. Coasting effect (CE) is reported in up to 30% of patients during the first month of treatment discontinuation. DTR tend to reappear, but recovery of ankle reflexes is uncommon.
To minimize the neurological side-effects of vincristine, the maximum single dose recommended is 1.4 – 2.0 mg/m2, regardless of body surface area. Currently there is no

pharmacological treatment for vincristine induced PN. The only way to manage symptoms is to reduce singe and total doses or to discontinue the therapy.
Vinblastine induced PN is like the PN observed with vincristine, though less severe. Hematological toxicity precedes neurotoxicity and treatment may be discontinued before PN has time to develop. (Argyriou et al, 2012)

There are several indications for vincristine in oncology such as acute lymphoblastic leukemia, neuroblastoma, Hodgkin's lymphoma and non-Hodgkin's lymphoma. VCR related neurotoxicity has been first reported the 1960s. It primarily causes axonal degeneration and delay in distal axon transportation. VCR has poor CNS penetration and the neurological symptoms are more prominent in the PNS. The neurotoxicity profile of VRC can be divided into four groups: peripheral neuropathy, central neuropathy, encephalopathy and cranial neuropathy. Early loss of deep tendon reflexes is the most common peripheral neuropathy. Other side-effects are paresthesia, cranial nerve palsies, gait disorders and brain dysfunction is most severe cases. Wrist and foot drop, weakness and optic neuropathy are less often seen. The side-effects appear 2-19 weeks after treatment and typically loss of DTR occurs first. The incidence varies greatly depending on age, dosage, duration of treatment, liver function, nutritional condition and simultaneous consumptions of other drugs such as methotrexate.
(Talebian, 2014)

2.4 Taxanes

Paclitaxel and docetaxel belong to the group of chemotherapy agents that are microtubule stabilizing agents (MTSAs). They are effective mainly in treatment of solid tumors. Taxanes have several side-effects but PN is the main adverse effect alongside with hematological toxicity.

The pathogenesis of neurological symptoms is induced by the action of disrupting microtubules of the mitotic spindle and the following interference of axonal transport, which can affect the soma of sensory neurons. A dying back process has been demonstrated starting in the distal nerve endings followed by a disturbed cytoplasmatic flow in the affected neurons.

PN is usually in the form of paresthesia, numbness or pain in a glove-and-stocking pattern. Decreased sense of position and vibration perception, loss of pain and temperature sensation

and DTR impairment are common findings in clinical examinations. Motor impairment with distal or proximal muscle weakness is less frequently observed.
Paclitaxel is more neurotoxic than docetaxel and is associated with a higher frequency of PN. The symptoms are highly correlated with the cumulative doses: Cumulative doses of 1000 mg/m2 for paclitaxel and 400 mg/m2 for docetaxel are reported to cause PN. Taxane induced PN resolves in 3-6 months but severe symptoms persist for a longer time and take longer to resolve. (Argyriou et al, 2012)

2.5 Clinical presentation

The typical presentation of CIPN is in a glove-and-stocking pattern. This is a symmetric, mainly sensory distal neuropathy. Most frequent symptoms are paresthesia, numbness and disturbances in balance. Paresthesia usually manifests as tingling, sharp pain and burning. Sometimes cranial involvement and prominent motor symptoms may accompany other symptoms. The intensity of symptoms varies greatly depending on which chemotherapy agents are used and how many treatment cycles in given in the schedule. Comorbid conditions and administration of more than one agent can intensify the neurological effects. (Stone, 2016)

Table 1. Risk factors and Medical Comorbidities Associated with Peripheral Neuropathy (Tzatha, 2016)

Prior exposure to neurotoxic agents
Diabetes
Vitamin deficiencies (B12 / Folate, B1, B6
Paraproteinemia
Thyroid dysfunction
Alcohol exposure
Preexisting hereditary neuropathy
Decreased creatinine clearance
Human immunodeficiency virus

A phenomenon where symptoms progress even when chemotherapy course has ended is called a coasting phenomenon. Drugs known to cause this phenomenon are cisplatin, oxaliplatin and

vincristine. Numerous genes have been investigated as an explanation for this symptom but the results were inconclusive. Genetic variations or polymorphism are currently considered to be the reason. CIPN is investigated mainly and graded mainly by questionnaires and clinical examinations performed by oncologists. The reporting remains subjective and limited because they rely on reporting of symptoms. Patients and healthcare professionals often have a different perception of symptoms. In certain professions where hand skills are particularly important the irreversibility of sensory and motor function might mean not being able to continue at work. (Abolfazl and Postma, 2014)

2.5.1 Chemotherapy induced peripheral neuropathy

The peripheral nervous system is more exposed to noxious substances than the central nervous system which is effectively protected. Nerve fibers and neuronal bodies (dorsal root ganglia of the primary sensory neurons) are frequently affected by the neurotoxic drugs. The clinical symptoms depend greatly on the agents used and the site of action. Symptoms varying from motor, to sensory-motor, to almost exclusively sensory neuropathies. Autonomic impairment may or may not be present. (Argyriou et al, 2012)

Chemotherapy induced peripheral neuropathy (CIPN) is a frequent side-effect of cancer chemotherapy. Agents known to cause CIPN include platinum containing substances (cisplatin and carboplatin), antitubulins (taxanes and vinca alkaloids), bortezomib which is a proteasome inhibitor, immunomodulatory agents (thalidomide, lenalidomide) and newer biological medications (alemtuzumab, iplimumab, brentuximab).

A research published recently indicates that CIPN prevalence in chemotherapy patients is 48%. After the 1st month of completing chemotherapy CIPN was present in 68.1% of patients. 6 months after the completion of chemotherapy the amount was reduced to 30% of patients. The data was reviewed from 31 meta-analysis studies which included data from 4,179 patients. The incidence CIPN varies greatly on the chemotherapy regimen. For instance, is it a monotherapy or are several drugs involved. Also, the duration of chemotherapy and exposure to neurotoxic substances has a strong correspondence. The way research evaluation methods of CIPN and studies may not be directly comparable with each other for this reason. In some patients, the side-effects caused by CIPN are so serious that they diminish the quality of life and may impact the everyday life of patients. Chemotherapy treatment can be discontinued or dose adjustments

can be made in case the polyneuropathy gets severe. Nowadays cancer survival rates are higher than before due to advances in treatment regimens. The quality of life is a major concern post chemotherapy and the long-term sequelae of CIPN has become increasingly important. (Cavaletti et al, 2015)

2.5.2 Chemotherapy induced ototoxicity

Tinnitus and permanent bilateral hearing loss are a severe side-effect of chemotherapy. Drugs which mainly induce ototoxicity are cisplatin and carboplatin from the platinum containing drugs group. They represent important challenges because there is a lack of ability to prevent and to reduce ototoxicity. Only a few studies have been made by applying modern approaches to understand the underlying mechanism. (Oldenburg, 2014)

Initially cisplatin hearing loss affects the higher frequencies but eventually affects the mid-range critical for speech perception. Long term tinnitus after cisplatin treatment affects 19% - 42% of patients and altered hearing thresholds affects 28% – 77% of patients depending on treatment time and intensity.

According to new research the pathogenesis lies in the overproduction of reactive oxygen species in the cochlea. This causes free radical-related apoptosis of outer hair cells, stria vascularis and spiral ganglion cells which are irreversible.

Objective measure of ototoxicity is recorded by air threshold audiometry which uses the frequencies 3000 Hz, 4000 Hz and 6000 Hz measured for both ears. They can be compared to normal age related audiograms and the variation is recorded. The frequencies best represent the upper hearing range of normal speech. (Travis, 2014)

2.5.3 Chemotherapy-induced nausea and vomiting

Chemotherapy-induced nausea and vomiting (CINV) is a common side-effect of tumor chemotherapy. This can significantly impact the quality of life and reduce therapy compliance as well as decrease the therapeutic effect. Only a few side effects are more feared by the patients than nausea and vomiting. CINV can be severe and distressing and a major concern for patients prior to initiation of therapy. CINV has been divided into three distinct types which has an important function for treatment and management. The first being acute (first 24h), but usually initiated in the first 1-2 hours and peaks at 5-6 hr. Delayed emesis occurs after the first 24hr

and anticipatory emesis occurs as conditioned response prior to initiation of therapy due to nausea and vomiting in previous treatments. (Chan et al, 2012)

2.5.4 Risk of CINV

The management of CINV has been greatly improved by the classification schemes that were initially developed in 1997. They were revised in 2004 Perugia Antiemetic Consensus Guideline meeting, though now more chemotherapy agents are available. They were divided into four different groups as described below. Two examples of I.V drugs are given in each group.

Table 2.1: Ematogenic risk of parenteral chemotherapy drugs

Emetogenic risk	% risk of emesis	Example of I.V drug
High	> 90	Cisplatin, cyclophosphamide (high dose)
Moderate	30-90	Carboplatin, doxorubicin
Low	10-30	Cabazitaxel, docetaxel
Minimal	< 10	Bevacizumab, vincristine

(National comprehensive cancer network, NCCN guidelines, April 2014)

The drug classification schema is utilized in both European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO). A separate classification is made for oral chemotherapy agents.

Table 2.3: Ematogenic risk for oral chemotherapy drugs

Ematogenic risk	% risk of emesis	Example of P.O drug
High	> 90	Altretamine, Procabazine
Moderate	30-90	Bosutinib, Certinib

Low	10-30	Afatinib, Axinitib
Minimal	< 10	Chlorambucil, Erlonitib

(MASCC/ESMO Antiemetic guideline 2016)

When using combination regimens and predicting how emetic the treatment is, the most emetic agent is identified from the combinations and the others are assessed for relative contribution. When taking two moderately emetic agents such as cyclophosphamide and doxorubicin and combining them the result is highly emetic. Though cyclophosphamide by itself in high doses is highly emetic. Also, anthracycline and cyclophosphamide as a combination is highly emetic. (Escobar et al, 2015)

The objective of antiemetic therapy is avoiding CINV completely and this should be achievable in most patients. Currently 5-HT3 receptor antagonists are clinically used and there have been improvements in the management of CINV. 5-HT3 receptor antagonists still have a deficit in the treatment of delayed vomiting caused by emetogenic chemotherapy drugs. Tropisetron, a commonly used 5HT-3 receptor antagonist, can effectively control 70% of acute CINV, but the effect on delayed vomiting is not conspicuous. Palonosetron which is a second generation 5-HT3 receptor antagonist has a longer half-life and a higher affinity to receptors, thus having a favorable effect on delayed nausea and vomiting. (Gralla et al, 2014)

In clinical settings only one antiemetic is usually used as CINV prevention. In a new study tropisetron and palonosetron were used as a combination treatment to see if there is a better response to prevent CINV than in monotherapy. Tropisetron and palonosetron as a combination proved to be more effective and safe in clinical controlling of CINV. Used together the effectiveness was 15.48% higher. First generation 5-HT3 receptor antagonists granisetron, ondansetron and tropisetron were all less effective in CINV prevention as tropisetron and palonosetron combined. They were effective in acute and delayed CINV. (Ma et al, 2015)

A triple therapy of aprepitant, palonosetron and dexamethasone has been investigated with medium and high ematogenic chemotherapy. The complete response (CR) rates were evaluated which means that there is clinically no nausea or salvage treatment. The acute phase means the first day of treatment and delayed phase includes days 2 to 5. The CR rates were 86% in general and 71% with patients receiving platinum containing drugs. CR in acute phase was 100% and in the delayed phase 71%. Most of the patients were able ingest food normally during the

treatment. The previous risk factor for CINV of patients did not prove to be clinically significant with platinum chemotherapy. (Yang, 2016) There risk factors are age, gender, prior nausea to initiation of therapy, history of drinking and prior motion sickness. Triple therapy can be recommended especially in high ematogenic cisplatin-based or carboplatin-based chemotherapy. (Kimura et al, 2015) (Peddi et al, 2014)

2.6 Prevention and management

The American Society of Clinical Oncology (ASCO) has produced new guidelines where anti-CIPN drugs are not recommended for neurotoxic cancer treatment. This is since there are no high-quality studies of CIPN prevention that would prove the efficacy. As treatment ASCO guidelines recommend duloxetine for symptomatic patients and drugs such as tricyclic antidepressants and gabapentin could be considered in addition. Tricyclic antidepressants (TCAs) and gabapentin do not have any effect on motor symptoms or negative sensory symptoms. Patients should be informed about lack of research on preventing CIPN and the possible additional costs it may add to the treatment.

There are some promising new developments in preventing neuroxicity when using platinum-based chemotherapy. Currently duloxetine is recommended for oxaliplatin therapy and it has proved to be efficient in CIPN prevention and safe for the patient. There is a genetic diversity between patients which modifies the drug response along with possible side-effects. For this reason, other platinum-based drugs do not have a drug for neuroprotection apart from oxaliplatin in which case duloxetine can be used. It is advised that a neuroprotection plan would be modified for each patient individually. Current studies recommend more research to be done in neuroprotection and to research the currently available drugs in more detail.
(Abolfazl et al, 2014)

Several studies have indicated that selenium is a neuroprotector. Selenium is an important trace element that we get in small dosages by diet. It scavenges free radicals and therefore has antioxidant and neuroprotective effects. Selenium is a cofactor for glutathione peroxidases (GPx). It protects DNA, protein and lipids by reducing hydro peroxidases and lipoperoxidases. Selenium is considered an important component of several selenoproteins which are expressed in the brain.

Chemo protective agents such as erythropoietin, vitamin E, valproate and melatonin have been used to prevent neurotoxic side-effects of platinum chemotherapy. In a new study, it is concluded that selenium may histopathologically and immunopathologically prevent the CNS side-effects that occur with platinum containing drugs. (Karavaelioglu, 2015)

2.7 Testing and diagnostics of CIPN

CIPN should be kept in mind before starting neurotoxic chemotherapy as well as during treatment. Early and prompt recognition is important to prevent worsening of symptoms and to avoid irreversible nerve damage. There are several laboratory tests that should be done in all patients prior to initiating neurotoxic chemotherapy: HbA1c (Glycohemoglobin) for diabetes screening, vitamin deficiencies (B12, B1), pyridoxine (B6) intoxication and thyroid abnormalities. Each of these states should be corrected prior to treatment if abnormalities are found. It is known that the loss of Achilles tendon reflex is the first clinical sign of CIPN. Thus, a basic neurological examination is performed in addition to the laboratory tests where sensory and motor status is recorded as well as deep tendon reflexes.
Small-fiber sensory function is assessed by measuring the threshold to detect warmth, hot and cold pain. Fibers that are thinly myelinated are assessed to detect skin cooling and sharpness. Cutaneous mechanical stimuli are detecting by assessing the large-fiber sensory function. (Carvalho Barbosa et al, 2014)

Knowing the diagnostics of CIPN are important, over diagnostics can potentially compromise treatment and negatively affect outcomes and survival. In a study where 55 female patients were treated for breast cancer were thought to have taxane-related polyneuropathy, in electrophysiological testing 67% had a large fiber polyneuropathy and 33% did not. In this example, it was important to know that chemotherapy can be continued in the 33% whose treatment would have otherwise been interrupted. Neurologic electrophysiological diagnostics play an important role in which defining the patients that actually have CIPN and the ones that do not.
In general, a neurologist is consulted only after symptoms have persisted for 6 months or longer. Patients with neurological predispositions are a more challenging group because CIPN might overlap with previous symptoms. Cervical or lumbar radiculopathy and compression neuropathies are good examples of preexisting conditions. Well tolerated neurological tests are nerve conduction studies (NCS) and electromyogram (EMG). There can be used as an accurate

objective tool for severity and to prognosticate recovery. A neurologist can assist in treatment options with for example a slow titration of gabapentin that is generally well tolerated. Duloxetine treatment is another good option providing moderate symptom relief. (Efstathia et al, 2016)

The clinical diagnosis is not generally difficult since nerve biopsies and neurophysiologic assessments can be made. These can help in evaluating pathological and functional nerve damage such as demyelinating versus axonal pathology. Objective electromyography of motor nerve excitability is a sensitive method to evaluate motor hyper excitability especially with oxaliplatin induced damage. The threshold tracking technique is used in assessment of axonal excitability. This can detect sensory axonal dysfunction before clinical symptoms appear and can be used as a predictive marker for nerve dysfunction.

CIPN is multidisciplinary medical issue which requires specialist from several fields of medicine. There are several questionnaires and scales used currently to assess CIPN: The Functional Assessment of Cancer Neurotoxicity scale, FACT-taxane scales and the Patient Neurotoxicity Questionnaire. EORTC questionnaires are widely used nowadays. There are vast differences in measuring and recording patient symptoms and the result depends greatly on which test or questionnaire is used. (Abolfazl et al, 2014).

3. Materials and methods

3.1 General Information

The study was done by using questionnaires inquiring about the neurological side-effects patients have during chemotherapy. The patients selected for the study had to be currently in chemotherapy treatment. Radiotherapy was an eliminating factor because results would be inconclusive if two different therapy modules were utilized at the same time. The place of data gathering was P. Stradins Clinical University Hospital Oncology department. The data was gathered during September 2016 till January 2017. The questionnaire was initially written in English and later translated in to Latvian and Russian. 200 patients were initially considered for the research before exclusion. 51 patients were selected to take part in the study. 30 patients were males and 21 females. Patients who were in generally good condition could fill the questionnaire on their own and the ones in weaker state were interviewed and the data was filled in together. Information regarding antineoplastic drugs and detailed information about the cancer was taken from patient files at the Oncology department. Oncology residents assisted with patient selection indicating which patients in the clinic were eligible for the study.
The research was approved by the ethics committee in September 2016.

3.2 Questionnaire

The questionnaire is divided in to five different segments. The first segment is about general information. Information taken was the personal code, year of birth, gender, height and weight. The height and weight will be used to calculate the body mass index (BMI) of each patient.
The second segment is concerning the information of chemotherapy. Information for this segment was taken from the patient files. The questions about chemotherapy inquire the name of the drug used and the total dose. The duration of chemotherapy treatment and number of chemotherapy cycles given. The year of cancer diagnosis and type of cancer with staging. Information also about the use of an antiemetic and painkillers.

The third segment is regarding neurological complications of chemotherapy. This section is divided into two sub segments: headache and polyneuropathies. The information about headache is evaluated by a numeric pain intensity scale which has numbers from 0 – 10. Zero (0) being no pain, five (5) being moderate pain and ten (10) being the worst possible pain. The

patients circled the number which corresponded to the amount of headache pain experienced during chemotherapy. The sub segment of polyneuropathies has two different images of human body front and back, and the purpose is for the patient to draw or circle the area where paresthesia or weakness was experienced. Paresthesia and weakness were evaluated separate on own images.

The forth segment focuses on the central nervous system (CNS) symptoms. First questions are regarding autonomic nervous system (ANS) sweating and freezing. They were evaluated as none, light, moderate and severe. Nausea and vomiting are evaluated on a 24-hour basis asking how many times has the patient been nauseous or vomited during the last 24 hours. The last question is about memory or concentration problems the patient might have had during the chemotherapy course.

The fifth segment is regarding any other neurological symptoms patients may have had during chemotherapy. Here patients could write freely in case there were other symptoms experienced.

3.3 Statistics

The statistics are made with Microsoft® Excel 2015 Mac and IBM® SPSS Statistics standard 23. A division that was made is according to difficulty to treat based on prognosis of cancer type. The cancer survival data is from Cancer Research UK and according to 1 year survival, patients were divided into two groups with mean survival of 70% as the cutoff point. The patients were placed in two groups labeled survival prognosis >70%, survival prognosis <70%. The cancers that have a better prognosis are breast (78% mean survival), prostate (84%), testicular cancer (98%) and melanoma (89%). The cancers with worse prognosis were lung (5%), colorectal (57%), urothelial (50%), ovarian (35%) and pancreatic cancer (1%), and non-Hodgkin's lymphoma (63%). (Cancer research UK, 2014).

The group with better prognosis has mean 1-year survival rate of > 70% and the group with worse prognosis has a mean 1-year survival rate of < 70%. In this way, the group with 1-year cancer prognosis >70% has n=15 subjects and the group with 1-year prognosis <70% has n=36 subjects.

In another division, patients are categorized in to two different groups dividing them in to platinum drug and non-platinum chemotherapy receiving groups. This way the we can analyze the hypothesis whether platinum drug based chemotherapy gave more neurological side-effects than non-platinum chemotherapy. Another group comparison is made with diving patients

according to BMI: Patients with BMI < 25 and patients with BMI > 25.1. This way we able to analyze whether BMI plays a role in incidence of neurological symptoms. Patients are also divided according to genders: male and female. There were 30 males and 21 females. The goal was to identify whether gender has significance in incidence and intensity of symptoms.

4. Results

4.1 Presence of the Headache

Table 4.1: Statistically Significant Difference in the Presence of the Headache of the two Medication Groups (Platinum, Non-platinum)

			Headache Presence (Yes/No)		
			No	Yes	Total
Medication (Platinum/Non-Platinum)	Platinum Containing	Count	13	23	36
		% within Medication (Platinum/Non-Platinum)	36,1%	63,9%	100,0%
		% within Headache Presence (Yes/No)	65,0%	74,2%	70,6%
		% of Total	25,5%	45,1%	70,6%
	Non-Platinum Containing	Count	7	8	15
		% within Medication (Platinum/Non-Platinum)	46,7%	53,3%	100,0%
		% within Headache Presence (Yes/No)	35,0%	25,8%	29,4%
		% of Total	13,7%	15,7%	29,4%
Total		Count	20	31	51
		% within Medication (Platinum/Non-Platinum)	39,2%	60,8%	100,0%
		% within Headache Presence (Yes/No)	100,0%	100,0%	100,0%
		% of Total	39,2%	60,8%	100,0%

In the table above is the comparison between headache incidence in platinum and non-platinum chemotherapy receiving groups. Platinum group had an incidence of 64.9% and less toxic group had 53.3%. Overall incidence was 60.8%.

The observed differences between the two groups regarding the presence of headache were statistically insignificant, since Asymp. (2-sided) (p value) > 0.05.

Presence of symptoms was analyzed with platinum and less toxic medication groups. In total seven different neurological parameters are considered. Pearson Chi-Square test was performed to analyze statistics. Asymp. (2-tailed) (p value) > 0.05 for all symptoms. Therefore, there were no statistically significant differences between the two groups, regarding the presence of symptoms.

Table 4.2: Statistically Significant Difference in the Presence of headache of the two BMI Groups (<=25, >25)

			Headache Presence (Yes/No)		
			No	Yes	Total
BMI(<=25 / >25)	BMI<= 25	Count	7	9	16
		% within BMI(<=25 / >25)	43,8%	56,3%	100,0%
		% within Headache Presence (Yes/No)	35,0%	29,0%	31,4%
		% of Total	13,7%	17,6%	31,4%
	BMI > 25	Count	13	22	35
		% within BMI(<=25 / >25)	37,1%	62,9%	100,0%
		% within Headache Presence (Yes/No)	65,0%	71,0%	68,6%
		% of Total	25,5%	43,1%	68,6%
Total		Count	20	31	51
		% within BMI(<=25 / >25)	39,2%	60,8%	100,0%
		% within Headache Presence (Yes/No)	100,0%	100,0%	100,0%
		% of Total	39,2%	60,8%	100,0%

Presence of headache was analyzed in the two BMI groups. Group with BMI <= 25 had a 56.3% incidence and the group with BMI > 25 had 62.9%. Overall incidence being 60.8%.

The observed differences between the two BMI groups regarding the presence of headache were statistically insignificant, since Asymp. (2-sided) (p value) > 0.05.

Presence of symptoms was analyzed in the BMI groups with seven different parameters. Asymp. (2-sided) (p value) > 0.05 for all symptoms. Therefore, there were no statistically significant differences between the two BMI groups, regarding the presence of symptoms.

4.2 Intensity of Symptoms

Table 4.3: Statistically Significant Difference in the Intensity of the Symptoms of the two Medication Groups (Platinum, Non-Platinum).

Ranks

	Medication (Platinum/Non-Platinum)	N	Mean Rank	Sum of Ranks
Headache Intensity (0-10)	Platinum Containing	36	26,61	958,00
	Non-Platinum Containing	15	24,53	368,00
	Total	51		
Sweating Intensity (0-3)	Platinum Containing	36	27,11	976,00
	Non-Platinum Containing	15	23,33	350,00
	Total	51		
Freezing Intensity (0-3)	Platinum Containing	36	27,07	974,50
	Non-Platinum Containing	15	23,43	351,50
	Total	51		

Test Statistics[a]

	Headache Intensity (0-10)	Sweating Intensity (0-3)	Freezing Intensity (0-3)
Mann-Whitney U	248,000	230,000	231,500
Wilcoxon W	368,000	350,000	351,500
Z	-,471	-1,010	-,866
Asymp. Sig. (2-tailed)	,638	,313	,387

a. Grouping Variable: Medication (Platinum/Non-Platinum)

In the table above headache, freezing and sweating intensity are statistically analyzed in the medication groups. No statistical correlation was observed between them ($p > 0.05$).

The observed differences between the two medication groups regarding the intensity of headache were statistically insignificant, since Asymp. (2-tailed) (p value) > 0.05.

Table 4.4: Statistically Significant Difference in the Intensity of the Symptoms of the two BMI Groups (<=25, >25)

Ranks

	BMI (<=25 / >25)	N	Mean Rank	Sum of Ranks
Headache Intensity (0-10)	BMI<= 25	16	25,31	405,00
	BMI > 25	35	26,31	921,00
	Total	51		
Sweating Intensity (0-3)	BMI<= 25	16	22,78	364,50
	BMI > 25	35	27,47	961,50
	Total	51		
Freezing Intensity (0-3)	BMI<= 25	16	28,06	449,00
	BMI > 25	35	25,06	877,00
	Total	51		

Test Statistics[a]

	Headache Intensity (0-10)	Sweating Intensity (0-3)	Freezing Intensity (0-3)
Mann-Whitney U	269,000	228,500	247,000
Wilcoxon W	405,000	364,500	877,000
Z	-,231	-1,277	-,729
Asymp. Sig. (2-tailed)	,817	,202	,466

a. Grouping Variable: BMI(<=25 / >25)

Intensity of headache, freezing and sweating was analyzed in the BMI groups.
Asymp. (2-tailed) (p value) > 0.05 for headache, sweating and freezing symptoms. Therefore, there were no statistically significant differences between the two BMI groups, regarding the presence of symptoms.

The observed differences between the two BMI groups regarding the intensity of headache were statistically insignificant, since Asymp. (2-tailed) (p value)> 0.05

4.3 Number of Symptoms

Table 4.5: Statistically Significant Difference in the Number of the Symptoms based on One-year survival prognosis.

Group Statistics

	Prognosis >70% / Prognosis <70%	N	Mean	Std. Deviation	Std. Error Mean
Total Number of Symptoms (0-7)	Prognosis >70%	15	1,60	1,805	,466
	Prognosis <70%	36	2,81	1,925	,321

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Total Number of Symptoms (0-7)	Equal variances assumed	,455	,503	-2,074	49	,043	-1,206	,581	-2,373	-,038
	Equal variances not assumed			-2,131	27,904	,042	-1,206	,566	-2,365	-,047

Significant results were observed in the Survival Prognosis groups regarding number of symptoms. Asymp. (2-tailed) (p value) < 0.05 for regarding one-year the survival prognosis of cancer and the number of symptoms. Therefore, patients with a longer life expectancy, have

significantly lower number of symptoms (mean rank 1,60) compared to those with shorter life expectancy (mean rank 2,81).

There were no statistically significant differences regarding medication and number of symptoms, BMI and number of symptoms or gender and number of symptoms.

4.4 Presence of headache in Survival Prognosis groups

Table 4.6: One-year Prognosis >70% / Prognosis <70% * Headache Presence (Yes/No)

			Headache Presence (Yes/No)		Total
			No	Yes	
Prognosis >70% / Prognosis <70%	Prognosis >70%	Count	9	6	15
		% within better / worse prognosis	60,0%	40,0%	100,0%
		% within Headache Presence (Yes/No)	45,0%	19,4%	29,4%
		% of Total	17,6%	11,8%	29,4%
	Prognosis <70%	Count	11	25	36
		% within better / worse prognosis	30,6%	69,4%	100,0%
		% within Headache Presence (Yes/No)	55,0%	80,6%	70,6%
		% of Total	21,6%	49,0%	70,6%
Total		Count	20	31	51
		% within better / worse prognosis	39,2%	60,8%	100,0%
		% within Headache Presence (Yes/No)	100,0%	100,0%	100,0%
		% of Total	39,2%	60,8%	100,0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	3,851[a]	1	,050		
Continuity Correction[b]	2,715	1	,099		
Likelihood Ratio	3,803	1	,051		
Fisher's Exact Test				,065	,050
Linear-by-Linear Association	3,776	1	,052		
N of Valid Cases	51				

a. 0 cells (,0%) have expected count less than 5. The minimum expected count is 5,88.

b. Computed only for a 2x2 table

In the group with one-year cancer survival prognosis > 70% had significantly less headache than the group with one-year survival prognosis < 70%.

4.5 Presence of Sweating in Survival Prognosis groups

Table 4.7: One-year Prognosis >70% / Prognosis <70% * Sweating Presence (Yes/No)

			Sweating Presence (Yes/No)		
			No	Yes	Total
Prognosis >70% / Prognosis <70%	Easy	Count	13	2	15
		% within Prognosis >70% / Prognosis <70%	86,7%	13,3%	100,0%
		% within Sweating Presence (Yes/No)	37,1%	12,5%	29,4%
		% of Total	25,5%	3,9%	29,4%
	Difficult	Count	22	14	36
		% within Prognosis >70% / Prognosis <70%	61,1%	38,9%	100,0%
		% within Sweating Presence (Yes/No)	62,9%	87,5%	70,6%
		% of Total	43,1%	27,5%	70,6%
Total		Count	35	16	51
		% within Prognosis >70% / Prognosis <70%	68,6%	31,4%	100,0%
		% within Sweating Presence (Yes/No)	100,0%	100,0%	100,0%
		% of Total	68,6%	31,4%	100,0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	3,212[a]	1	,073		
Continuity Correction[b]	2,134	1	,144		
Likelihood Ratio	3,555	1	,059		
Fisher's Exact Test				,102	,068
Linear-by-Linear Association	3,149	1	,076		
N of Valid Cases	51				

a. 1 cells (25,0%) have expected count less than 5. The minimum expected count is 4,71.

b. Computed only for a 2x2 table

Regarding presence of autonomic nervous system induced sweating in prognosis groups no significant results ($p > 0.05$) were observed.

4.6 Presence of Freezing in Survival Prognosis groups

Table 4.8: One-year Prognosis >70% / Prognosis <70% * Freezing Presence (Yes/No)

			Freezing Presence (Yes/No)		
			No	Yes	
Prognosis >70% / Prognosis <70%	>70%	Count	11	4	15
		% within Prognosis >70% / Prognosis <70%	73,3%	26,7%	100,0%
		% within Freezing Presence (Yes/No)	42,3%	16,0%	29,4%
		% of Total	21,6%	7,8%	29,4%
	<70%	Count	15	21	36
		% within Prognosis >70% / Prognosis <70%	41,7%	58,3%	100,0%
		% within Freezing Presence (Yes/No)	57,7%	84,0%	70,6%
		% of Total	29,4%	41,2%	70,6%
Total		Count	26	25	51
		% within Prognosis >70% / Prognosis <70%	51,0%	49,0%	100,0%
		% within Freezing Presence (Yes/No)	100,0%	100,0%	100,0%
		% of Total	51,0%	49,0%	100,0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4,249[a]	1	,039		
Continuity Correction[b]	3,076	1	,079		
Likelihood Ratio	4,382	1	,036		
Fisher's Exact Test				,064	,039
Linear-by-Linear Association	4,165	1	,041		
N of Valid Cases	51				

a. 0 cells (,0%) have expected count less than 5. The minimum expected count is 7,35.

b. Computed only for a 2x2 table

The group with one-year cancer survival prognosis > 70% had a 26.7% incidence in presence of freezing and the group with < 70% one-year prognosis had a 58.3% incidence. The results are statistically significant (p = 0.039) and longer survival prognosis group has significantly less ANS freezing as a side-effect.

4.7 Intensity of Symptoms in Survival Prognosis groups

Table 4.9: One-year Prognosis >70% / Prognosis <70% and Intensity of symptoms

Ranks

	Prognosis >70% / Prognosis <70%	N	Mean Rank	Sum of Ranks
Headache Intensity (0-10)	>70%	15	19,20	288,00
	<70%	36	28,83	1038,00
	Total	51		
Sweating Intensity (0-3)	>70%	15	21,40	321,00
	<70%	36	27,92	1005,00
	Total	51		
Freezing Intensity (0-3)	>70%	15	20,37	305,50
	<70%	36	28,35	1020,50
	Total	51		

Test Statistics[a]

	Headache Intensity (0-10)	Sweating Intensity (0-3)	Freezing Intensity (0-3)
Mann-Whitney U	168,000	201,000	185,500
Wilcoxon W	288,000	321,000	305,500
Z	-2,183	-1,742	-1,900
Asymp. Sig. (2-tailed)	,029	,082	,057

a. Grouping Variable: Easy / Difficult to Cure

Regarding One-year Survival Prognosis and Intensity of symptoms

1. For Headache asymp. Sig. (p value) = 0.029 which indicates that patients who have one-year survival prognosis >70%, have significantly lower intensity of headache.
2. For Sweating and Freezing, Asymp. Sig. (p value) > 0.05 which indicates that for this sample size no significant difference is observed.

However, Asymp. Sig. is close to 0.05 therefore a larger sample size is possible to indicate statistically significant differences.

There is a possibility that sweating and freezing will be more intense to patients who are difficult to cure and that can be a subject of further research.

Regarding Gender and Intensity of Symptoms, there were no significant results were observed.

5. Discussion

In this research, the focus was on identifying and finding the incidence of neurological side-effects and comparing the two main patient groups, one with one-year survival prognosis >70% and the second with one-year survival prognosis of < 70%. All the patients in the research were receiving painkillers and anti-emetics before and during treatment. Also, all the cancers were initially diagnosed in the year 2016.

The types of cancers treated with chemotherapy were divided into two groups according to cancer prognosis and how successful treatment is in general according to research. Statistical correlation was found in total number of symptoms observed. Seven different parameters were evaluated: headache, paresthesia, weakness, sweating, freezing, nausea and vomiting. The group with better cancer prognosis had a mean number of 1.60 (SD ± 1.805) in number of neurological symptoms and group with shorter life expectancy had a mean number of 2.81 (SD ± 1.925), (p = 0.043). This result is significant and it can be concluded that the group with longer life expectancy has significantly less symptoms than the group with shorter life expectancy.

Presence of headache was statistically tested on the same groups (survival prognosis >70% / <70%). The survival group >70% had a 40% (n=6) incidence in headache and survival <70% group had 69.4% (n=25) incidence (p= 0.050). The result is significant and it can be concluded that cancers with a shorter survival prognosis have a greater incidence of headache during chemotherapy.

Presence of sweating was tested on the same group and the group with a longer survival prognosis had 13,3% (n=2) and shorter survival prognosis group had 38,9% (n=14) incidence (p = 0.073). The result is potentially significant and could be recommended for further research. There is a possibility that sweating will appear more often to patients who have a shorter life expectancy and that can be a subject of further research.

Presence of autonomic nervous system induced freezing in the survival prognosis >70% group was 26,7% (n=4) and in prognosis <70% to treat group 58,3% (n=21) (p = 0,039). The results are significant and it can be said that shorter life expectancy group have significantly more freezing as a side-effect than shorter life expectancy group.

Regarding prognosis and intensity of symptoms, for headache asymp. Sig (p value) < 0.05 which indicates that patients who have a longer one-year survival prognosis, have significantly

lower intensity of headache symptoms. Mean rank in the longer survival group was 19,20 and 28,83 in the shorter survival group (p = 0,029).

For Sweating and Freezing, Asymp. Sig. (p value) > 0.05 which indicates that for this sample size no significant difference is observed. However, Asymp. Sig. is close to 0.05 therefore a larger sample size is possible to indicate statistically significant differences. Sweating intensity in the longer survival group was 21,40 and shorter survival 27,94 (p = 0,082). Freezing intensity mean rank in the longer survival group was 20,37 and in the shorter survival group it was 28,35 (p = 0,057). There is a possibility that sweating and freezing will be more intense to patients with shorter life expectancy and that can be a subject of further research.

In the parameter of headache, the platinum group had a 63,9% (n=23) incidence in headache and non-platinum group had 53,3% (n=8) incidence. The result is insignificant (p > 0.05), however, more headache was reported in the platinum group.

Headache was reported on a scale of 0 – 10 to find significant differences between platinum and non-platinum groups. There were no significant differences (p > 0.05). However, platinum group had a mean rank of 26,61 and non-platinum had a mean rank of 24,53. Greater differences were observed in the intensity of sweating and freezing. Sweating mean rank of platinum group was 27,11 and non-platinum 23,33 (p > 0.05). Platinum group had insignificantly more sweating as a side-effect. Mean rank in the intensity of freezing in the platinum group was 27,07 and non-platinum 23,43 (p = 0,387). The platinum group experienced more freezing but the results are insignificant.

No significant correlation was observed within the groups regarding paresthesia or weakness (p > 0.05). Platinum and non-platinum groups both had a similar 33.3% incidence in weakness. The platinum group had 30.6% (n=11) and non-platinum group had 26.7% (n=4) incidence in paresthesia. CIPN prevalence in chemotherapy patients is 48% according to a larger research (Cavalletti, 2010). The percentage increases after cessation of chemotherapy. It may be that if patients were followed up for a longer period and a new questionnaire would be filled after chemotherapy, a correlation between the groups may be found.

In a study the effects and side-effects of platinum drugs were compared against non-platinum drug. Here major differences were observed also between cisplatin and carboplatin, with cisplatin giving significantly higher incidences in nausea and vomiting (p = 0.05). Also, cisplatin receiving patients were more symptomatic in general compared to non-platinum receiving patients. (Rajeswaran and Trojan, 2008). It may be that since in this research platinum

drugs were not compared against each other but instead as a group of platinum containing drugs, the results are insignificant. If cisplatin would have been compared separately to other agents, there may have been significance in results. Also, the coasting effect must be taken under consideration since the PN induced by platinum compounds may progress months after cessation of chemotherapy.

Patient were divided into two groups according to BMI, to see if there is any correlation with BMI and neurological side-effects. One group with BMI <= 25 (n = 16), and the second with BMI > 25 (n = 35). There were no significant results between the groups in presence of headache ($p > 0,05$). Group with BMI <= 25 had 56,3% incidence and the group with BMI > 25 had 62,9% incidence.
Intensity of headache between the BMI groups was insignificant ($p > 0,05$). Mean rank of BMI <= 25 was 25,31 and BMI > 25 was 26,31. Sweating intensity mean rank in BMI <= 25 was 22,78 and BMI > 25 was 27,47 ($p = 0,202$). Intensity of freezing mean rank in BMI <= 25 group was 28,06 and in BMI > 25 group 25,06 ($p = 0,466$). Results of sweating and freezing intensities between groups were insignificant but it should be notes that more sweating was recorded in the BMI > 25 group and more ANS freezing in the BMI <= 25 group.

In the BMI groups nausea and vomiting correlation was insignificant ($p > 0.05$).
Nausea and vomiting have been reported in another study where BMI 18.5 kg/m2 was the dividing value for two groups. Both nausea ($p = 0.066$) and vomiting ($p = 0.140$) were insignificantly higher in the low BMI group. (Chatterjee and Roy, 2014). Since all patients were using anti-emetics this may affect the result and no clear trends are seen within the groups. The fact that in the mentioned research had a lower BMI dividing point than in this research the patients had more side-effects due to being underweight.

Presence of paresthesia in the BMI groups was insignificant ($p > 0.05$). The group with BMI <=25 had an incidence of 37.5% (n=6) and group with BMI > 25 had a 25.7% (n=9) incidence. There is no statistical correlation between BMI and presence of paresthesia ($p > 0.05$). Similar results were observed in a recent study where BMI 18.5 kg/m2 was diving factor in adverse drug reaction from platinum chemotherapy. In the results paresthesia was insignificantly higher in low BMI group ($p = 0.128$). (Chatterjee and Roy, 2014) In another study where chemotherapy dosing is under review, it is concluded that the dose is adjusted to body surface area (BSA). This is calculated from a function of weight and height (Favre, 1996). It is proposed that BSA does not fully correlate with cytotoxic drug elimination and can lead to unpredictable

variations in drug effect. Overdosing is easier to recognize and under dosing may be more common in practice, leading to patients not having a sufficient dose of drugs. (Gurney, 2002). The presence of weakness within the BMI groups was insignificant ($p > 0.05$). Incidence on weakness in BMI <= 25 group was 25% (n=4) and in BMI > 25 group 37.1% (n=13). It can be concluded that the group with BMI > 25 had an insignificantly greater incidence in weakness.

There were no statistically significant differences regarding medication and number of symptoms, BMI and number of symptoms or gender and number of symptoms ($p > 0.05$).

One of the short comings of the research is the number of subjects. A better result would have been achieved by increasing the number of subjects and this would have affected especially the comparison in medications groups and the prognosis groups. Several results in the prognosis groups were potentially significant and a larger number of subjects may increase the significance.

The prognosis of cancer was not calculated with the TNM staging system but instead by the type of cancer and one-year prognosis according to Cancer Research UK. The number of subjects would have been too small to gain any significant results with TNM staging system so for this reason the general one-year prognosis was implemented.

Another short coming is that the neurological side-effects were reported by the patients and not recorded by best neurological means. For instance, paresthesia and weakness can be recorded by electromyography (EMG) to have a better scientific result.

All the patients were receiving anti-emetics and pain killers during treatment and this greatly affects the results. In current literature, platinum (especially Cisplatin) should have a higher incidence in CINV than less toxic chemotherapy but in the results the was no significance. However, it is beneficial for the patients that they are not experiencing as much CINV and headache as literature would suggest.

There is more research to be done in prevention both peripheral and central neurological side-effects in chemotherapy. Currently the best means to counteract the side-effects is to reduce chemotherapy dosage or to discontinue treatment. Duloxetine is recommended for prevention of neurological side-effects in oxaliplatin therapy. For cisplatin, there isn't a regime as effective for preventing the neurotoxic effects.

The very old population (>70 years) is often underrepresented in chemotherapy studies and is an eliminating factor in patient selection. It would be recommended to research the neurological

side-effects this population also in more detail as increasing age often decreases tolerance to antineoplastic therapy.

There is a tendency that neurological side-effects are overlooked since hematological and gastrointestinal side-effects are more easily diagnosed and treated. Bone marrow suppression is one of the most common hematological side-effects but it can be overcome by growth factors or bone marrow transplantations. Neurological symptoms may go unnoticed unless patients actively report their symptoms or they are specifically asked by treating staff.

We can use these results in daily practice of Oncological chemotherapy, by prescribing preventively analgesics in “heavy” prognosis patients and autonomic nervous system stabilizers (Fenibut) in the same group patients with potentially serious freezing/sweating, improving their quality of life. There is no need to implement these measures in patients with a longer life expectancy. There are potential economic savings if neurological side-effects are prevented from the beginning in the risk groups.

6. Conclusions

1) The group with < one-year survival prognosis of cancer has statistically significantly more neurological symptoms in total than the group with longer survival prognosis.

2) The group with < one-year prognosis has statistically significantly more incidence in headache than the group with longer survival prognosis.

3) There is a possibility that sweating and sensation of freezing induced by autonomic nervous system will be more intense to patients with shorter one-year survival prognosis.

4) Patients with worse prognosis cancers have a statistically higher incidence of autonomic nervous system freezing than in cancer that have a better prognosis.

5) There are no statistically significant differences regarding chemotherapy medication and number of neurological symptoms, BMI and number of neurological symptoms or gender and number of neurological symptoms.

6) No significant correlation was observed within platinum and non-platinum based chemotherapy groups regarding neurological side-effects.

7) We can use these results in daily practice of Oncological chemotherapy, by prescribing preventively analgesics in < one-year survival prognosis patients and autonomic nervous system stabilizers in the same group patients with potentially serious freezing/sweating. It could improve their quality of life. There is no need to implement these measures in patients with a longer life expectancy.

8) We conclude that there is no need to preventively treat patients depending on gender, BMI, chemotherapy drug regime.

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Atte Laurila

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9. Appendix

English Questionnaire

Atte Laurila
M.D Ainars Gailitis
Latvian University
Department of Neurology

Questionnaire for Academic Research in Oncology

General information:

1. Personal code _____
2. Year of birth _____
3. Gender Male Female
4. Height and weight _____

Chemotherapy information:

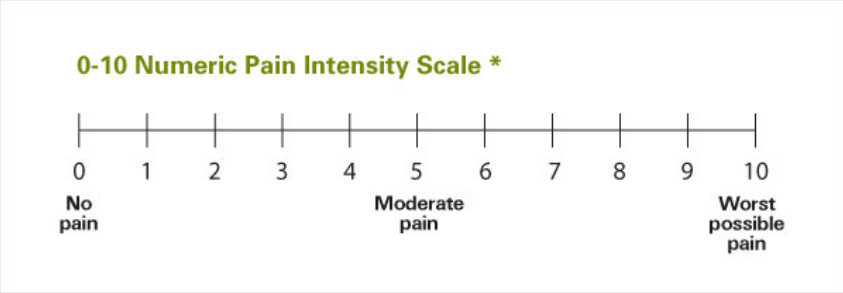
1. Name of chemotherapy drug and total dose
   _____
2. Duration of chemotherapy treatment? Nr. of cycles?
   _____
3. Which year was cancer diagnosed?
   _____
4. Type of cancer and stage (I-IV)?
   _____
5. Antiemetic used?
   _____

6. Painkillers used?

_____

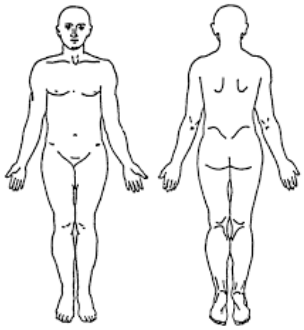
Neurological side-effects of chemotherapy:

5. Headache

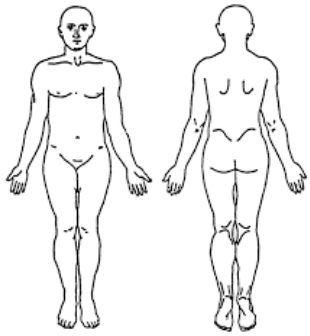


6. Polyneuropathies

A. Paresthesias (Show where)
(Loss of sensation)



B. Weakness (Show where)



C. **Autonomic Nervous System symptoms**

Sweating, freezing (light, moderate, severe)

7. **Nausea**: How often? / 24h

8. **Vomiting**: How often? / 24h

9. **Memory or concentration problems**?

(Short tests)

Other side effect symptoms of chemotherapy if any

_____

_____

Latvian Questionnaire

Atte Laurila
M.D Ainārs Gailītis
Latvijas Universitāte
Neiroloģijas departaments

Aptauja akadēmiskajam pētījumam onkoloģijā

Vispārēja informācija:

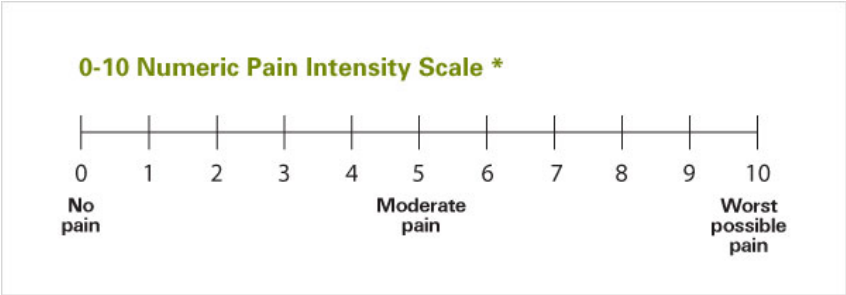
1. Personas kods _____
2. Dzimšanas gads _____
3. Dzimums Vīrietis Sieviete
4. Garums un svars _____

Ķīmijterapijas informācija:

1. Ķīmijterapijas zāļu nosaukums un kopējā deva
_____
2. Ķīmijterapijas ārstēšanas ilgums? Ciklu skaits?
_____
3. Kurā gadā vēzis tika diagnosticēts?
_____
4. Vēža tips un stadija (I-IV)?
_____
5. Vai tika lietoti antiemētiskie (pretvemšanas) līdzekļi?
_____
6. Vai tika lietoti pretsāpju līdzekļi?
_____

A. Ķīmijterapijas neiroloģiskie blakus efekti:

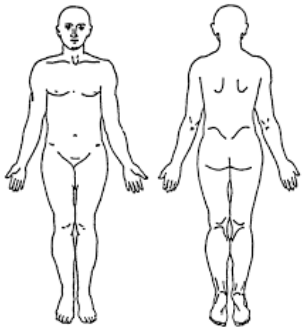
1. **Galvas sāpes**



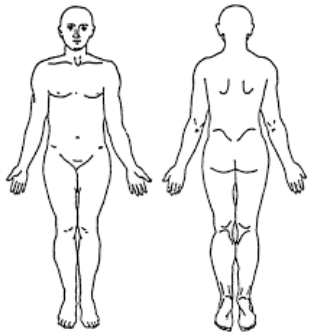
(0-10 sāpju intensitātes skala, 0- nekādu sāpju, 5- mērenas sāpes, 10- stiprākās iespējamās sāpes)

2. Polineiropātija

Parestēzija (parādiet uz zemāk redzamā attēla kur)
(Sajūtu zudums)



3. **Vājums** (parādiet uz zemāk redzamā attēla kur)



D. **Anatomiskās nervu sistēmas simptomi**

Svīšana, salšana (viegla, vidēja, stipra)
_____

4. **Nelabums**: Cik bieži? / 24h
   _____
5. **Vemšana**: Cik bieži? / 24h
   _____
6. Atmiņas vai koncentrācijas problēmas?
   (Īsi testi)

Citi ķīmijterapijas blakus efekti, ja bija kādi?

_____
_____

Russian Questionnaire

Atte Лаурила
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Общая информация:

5. Персональный код _____
6. Год рождения _____
7. Пол Мужчина Женщина
8. Рост и вес _____

Информация о химиотерапии:

1. Название лекарства химиотерапии и общая доза?

_____

2. Продолжительность лечения химиотерапии? Количество циклов?

_____

3. В каком году был диагностирован рак?

_____

4. Тип рака и стадия (I-IV)?

_____

5. Были ли использованы антиэметики (противорвотные препараты)?

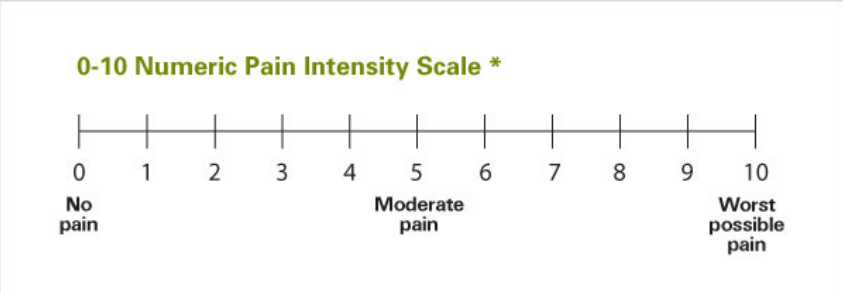
_____

6. Были ли использованы обезболивающие?

_____

Неврологические побочные эффекты химиотерапии:

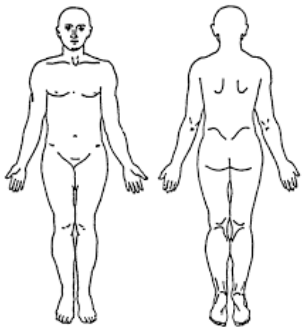
7. **Головная боль**



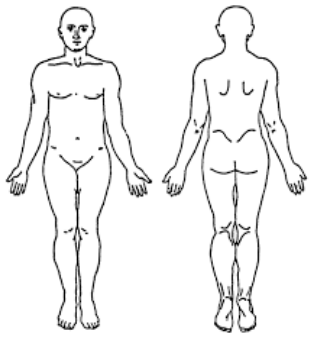
(Шкала интенсивности боли (0-10), 0-нет боли, 5- умеренная боль, 10- худшая возможноя боль)

8. **Полиневропатии**

A. **Парестезии** (Отметьте на картинке ниже)
(Потеря чувствительности)



B. **Слабость** (Отметьте на картинке ниже)



C. **Симптомы вегетативной нервной системы**

Потение, чувство холода (легкая, умеренное, сильная) _____

9. **Тошнота:** Как часто в сутки? _____
10. **Рвота:** Как часто в сутки? _____
11. **Проблемы с памятью или концентрацией?** _____ ____
    (Короткие тесты)

Другие симптомы побочных эффектов химиотерапии, если таковые имеются

_____
_____

Documentation page

The Diploma Thesis,

„ Neurological side-effects of chemotherapy in Oncology, their dependence from cancer prognosis severity, BMI, gender and chemotherapy regimen, possibility to reduce side effects"

was developed at the Faculty of Medicine of the University of Latvia.
With my signature I attest, that this research has been carried out without aid or assistance. Used information was obtained only from indicated sources and the electronically submitted copy of this diploma work complies with the printout. I recommend the work for presentation.

Author: Atte Laurila _____
(name, surname) (signature)

Supervisor: Pasniedzējs Ainārs Gailītis _____, _____
(position, name, surname, degree) (signature), (date)

Reviewer: _____ _____, _____
(position, name, surname, degree) (signature) (date)

The diploma thesis was submitted to the Faculty of Medicine on: _____
(date)

International students' coordinator, Inese Vēvere: _____
(signature)

The diploma thesis is presented at the meeting of the State Examination Commission of Higher Professional Study Program "Medicine" _____2017. Protocol No. _____

Secretary of Commission: _____ _____
(position, name, surname, degree) (signature)