Cover page

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Chronic neuropathy following chemotherapy

Background

Peripheral neuropathy is a well-known side effect of chemotherapy(1). With an increasing number of cancer survivors receiving adjuvant chemotherapy, this complication represents a significant problem since chemotherapy-induced peripheral neuropathy (CIPN) affects physical, emotional, and cognitive functioning in cancer survivors, and thus their quality of life, and may be associated with pain(2, 3).

Most previous studies on CIPN have graded neuropathy using the National Cancer Institute, Common Toxicity Criteria (NCI-CTC v3.0) with a range of grades from 0 (no problem at all) to 4 (extensive problems interfering with activities of daily living). This rough grading scale has well-known limitations(4). Despite the introduction of different scales, only a few studies have described various types of pain and distinguished CIPN-related pain from other pain types(5, 6).

Several studies have explored the incidence, predictors, and impact of CIPN, but less is known about CIPN-related pain(7, 8). Most studies have pooled patients with different types of cancer treated with different neurotoxic agents(9, 10), which complicates the interpretation of the results, since the incidence and type of CIPN are dependent on the specific chemotherapeutic agent used(11). Additional therapies such as surgery, radiation therapy, and endocrine therapy can cause other types of neuropathy and pain(12) and are used to varying degrees, but this has rarely been discussed.

Neuropathic pain/painful polyneuropathy: The most common disabling condition of chemotherapy-induced peripheral neuropathy is neuropathic pain(13). Neuropathic pain is not a term applied to a single underlying mechanism or disease, but describes a syndrome of various sensory symptoms and signs (e.g. spontaneous ongoing pain, allodynia and painful attacks). Patients treated with the chemotherapeutic drug oxaliplatin for colorectal cancer experience acute onset of perioral and distal paresthesia and a very characteristic and disabling cold allodynia. These symptoms are most severe immediately and in the first days after the chemotherapy and then gradually subside, and are usually reversed at the time of the next treatment. Later on, the patients may develop a cumulative sensory axonal polyneuropathy with vibration deficits, numbness and distal paresthesia or pain. Docetaxel a chemotherapeutic drug used in the adjuvant treatment of high-risk breast cancer, also has dose limiting side-effects

including hematologic depression occurring around the first 2 weeks after a cycle and chronic peripheral neuropathy.

Ion channels and pain: The transmission and processing of pain signals rely critically on the activities of ion channels that are expressed in afferent pain fibers(14). Abnormal ion channel expression following nerve injury results in enhanced neuronal excitability that underlies ongoing and evoked neuropathic pain, and sodium, calcium, potassium and chloride channels are emerging as attractive targets for the treatment of pain(14). It is likely that certain pain phenotypes are related to specific changes in ion channels.

Threshold tracking: Axonal excitability testing using the threshold tracking technique provides complementary information to conventional nerve conduction studies and may be used to infer the activity of a variety of ion channels, energy-dependent pumps and ion exchange processes activated during the process of impulse conduction(15, 16)

This protocol describes a clinical study, which we wish to add to an ongoing prospective questionnaire study. The study enrolled 174 patients aged ≥ 18 years who were treated with standard adjuvant capecitabine and oxaliplatin (Xelox) after high-risk colorectal cancer or standard docetaxel for high-risk breast cancer in the period of 2011 and 2012. Patients completed a questionnaire before, during and after treatment. The first part of the study is published (17). We found that chronic CIPN symptoms (tingling and/or numbness) in the feet at 1-year follow-up were present in 63.6% of patients without pre-existing neuropathy in the oxaliplatin group and in 44.8% in the docetaxel group, while pain in hands and feet was found in 31.3% and 35.1%, respectively. While the symptoms were very different between the two types of chemotherapy in the acute phase, neuropathy symptoms were more similar in the chronic phase. The CIPN affected the quality of life, but the general health was high (17).
The questionnaire study includes an additional follow-up postal questionnaire to surviving patients, which we will send out early 2016. In addition, and hence this protocol, we would like to conduct a clinical study to be able to diagnose neuropathy using clinical examination, corneal confocal microscopy, and neurophysiology, and to describe the sensory phenotypes and excitability changes in more detail using quantitative sensory testing and threshold tracking. The

present follow-up is part of the DOLORisk project: Understanding risk factors and determinants for neuropathic pain funded by the European Commission Horizon 2020 (ID633491), a collaboration between several European Universities.

Hypotheses for the clinical study

1. Chronic neuropathy following treatment with oxaliplatin and docetaxel is a length-dependent, sensory, axonal neuropathy characterized mainly by sensory loss. 2. There is a positive correlation between greater neuropathy severity and the presence and severity of neuropathic pain

Methodology and Research Plan

Patients and controls and inclusion and exclusion criteria

This is a follow-up study of a prospective questionnaire study(17) approved by Datatilsynet (J.nr. 2011-41-5725) and Sundhedsstyrelsen (videregivelse af oplysninger fra patientjournal) (Sagsnr. 3-3013-605/1). The study enrolled 174 patients aged ≥ 18 years who where treated with standard adjuvant Capecitabine and oxaliplatin (Xelox) after high-risk colorectal cancer or standard docetaxel for high-risk breast cancer in the period of 2011 and 2012.

The exclusion criteria were:

- Known metastatic cancer,
- Previous treatment with chemotherapy,
- Patients who do not speak, read or understand Danish

The patients received a specially designed questionnaire at baseline, after the 1st cycle of neurotoxic chemotherapy, midway in the adjuvant treatment, after one year. 93% (67 of 74 who received oxaliplatin and 94/100 who received docetaxel) responded after one year.

This study is a 5-year follow-up study, where we will send the questionnaire to all surviving patients who participated in the study. The questionnaire study(17) included 44 men and 30 females with an average age of 62.5 years (SD 8.4 years) in the group of colon cancer and 100 females with an average age of 51.6 years (SD 7.7 years) in the group of breast cancer. These will be asked if we may contact them with information on the clinical study. We expect that 60% in

the oxaliplatin group and 75% in the docetaxel group are alive and willing to participate, i.e. around 30 patients in each treatment group in the clinical study.

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These patients will participate in a one-session clinical study, which will include questionnaires and examinations to determine the presence of neuropathy by clinical examination, neurophysiological assessment, Quantitative Sensory Testing (QST), Nerve Conduction Studies (NCSs), Treshold Tracking, and Corneal Confocal Microscopy (CCM). The exclusion criteria for the 5-year follow-up questionarieis: if they are dead. The exclusion criteria for the clinical examination is: if they are not able to visit the Danish Pain Research Center or dead.

Methods

A follow-up questionnaire containing questions on pain, sensory abnormalities, mood, sleep, and quality of life, similar to previous questionnaires sent out to this population (Appendix 1), will be send out early 2016, with one reminder to non-responders.

At the end of the questionnaire, the two patient groups that have received chemotherapy (oxaliplatin or docetaxel), will be asked if we may contact them with information on a clinical study and if so, we ask them to provide their preferred contact details and preferred way of contact (mail, email or telephone) (see document "rekrutteringsmateriale"). After accepting contact regarding information about the clinical study, we will contact them via their preferred way of contact with short information. If they are interested in more information, we will send them the written patient information. If they are still interested, they will be invited to a visit at the Danish Pain Research Center, where they will receive the oral information as described under "*Enlistment of the participants and guidelines for oral participation information*".

Procedures

A medical and pain history will be taken and a neurological examination including mapping of sensory abnormalities will be performed. In addition, patients will be asked about alcohol and smoking consumption, medication use, family history of pain and neuropathy, trauma, physical activity, anxiety and depression symptoms and sleep disturbance. For case definition of neuropathy, we will use Tesfaye et al. 2010(18)

Questionnaires

Patients will fill out following questionnaires:

The Douleur Neuropathique 4 Questions (DN4) (19), which includes various pain descriptors and a small clinical examination, which will be performed by the investigator (see appendix 2).

The Neuropathic Pain Symptom Inventory (NPSI) (20), where patients rate the intensity of various pain descriptors (see appendix 3).

The Pain Catastrophizing Scale (PCS)(21). The questionnaire includes 3 dimensions: rumination, magnification, and helplessness. In addition, a total score indicates the level of pain catastrophizing (see appendix 4).

The PainDETECT (22). PainDETECT comprises questions on specific neuropathic pain symptoms, (see appendix 5).

The Michigan Neuropathy Screening Instrument (MNSI) (23) consist of 15 questions on foot sensation (pain, numbness, and sensitivity to temperature) (see appendix 6).

Quantitative sensory testing (QST): By using standardized QST, which assesses functional characteristics of both small and large afferent fibers by examining mechanical detection and pain thresholds, thermal detection and pain thresholds, and dynamic mechanical allodynia, the profile of sensory symptoms can be elucidated in each patient on the foot.

QST examinations will take approximately 3/4 hours.

Corneal Confocal Microscopy (CCM) is a new promising non-invasive tool to assess fiber loss at an early stage of polyneuropathy. The main CCM parameters to be analyzed are (a) corneal nerve fiber length (NFL), defined as the absolute length of nerves and branches per mm^2, (b) nerve fiber density (NFD), defined as the total number of major nerves per mm^2 and (c) nerve fiber branching (NFB), defined as the number of branch points per mm^2 (24, 25). CCM examinations will take approximately ½ hour.

Neurophysiological Examinations:

Nerve conduction studies (NCSs): Motor NCSs in peroneal, tibial and median nerves and sensory NCSs in sural and median nerves using conventional procedures with surface electrodes and a standard electromyography machine will be performed. NCSs will be used for diagnosis and staging of chronic neuropathy(26).

Threshold tracking

Motor and sensory excitability tests (threshold tracking) will be performed on the median nerve at the wrist using a computerized program (TRONDNF, Institute of Neurology, London, UK) as described previously(15). Multiple excitability parameters will be assessed included 1) Stimulus response curve to define the amplitude of the target response, 2) strength–duration time constant, a measure of passive membrane properties and nodal persistent Na^+ conductance; 3) threshold electrotonus, a measure of internodal conductances and membrane potential and 4) recovery cycle of excitability, an assessment of the recovery of excitability following an action potential marking the function of nodal Na^+ channels. Additionally, using a more detailed stimulus response curve called MScan, the number of motor units will be estimated.
Neurophysiological examinations will take approximately 1½ hours.

Screening tools

We will use following screening tools for neuropathy, and the assessments described in these are all part of the standard clinical neurological examination:

- The Toronto Clinical Scoring System (TCSS)(Bril & Perkins, 2002) (Appendix 7).
- Total Neuropathy Score (Appendix 8).
- NCI-CTC _ National Cancer Institute–Common Toxicity Criteria (Appendix 8).
- The Michigan Neuropathy Screening Instrument (Appendix 6).

Blood samples and biobank

We will collect blood (10ml) from each subject, which will be stored at -80^0C in a locked freezer. All samples will eventually be transported to the research lab led by Prof Mark McCarthy based at the University of Oxford, UK for storage in compliance with The Human Tissues Act and EU. DNA

will be taken for studies in genetics polymorphisms or mutations within genes that may modify the risk of a person developing a neuropathic pain and/or the severity of neuropathic pain, if and only if the patient agrees. Genetic analysis will be strictly restricted to the neuropathy and neuropathic pain field.

Character of planned bioinformatic analyses:
A genome wide association study will be performed. This will look at variants that are common in the general population.
Candidate gene analysis: This will be to look at genes previously implicated in pain such as voltage gated sodium channels and potassium channels. These genes have a role in pain only and not in other diseases such as e.g. inherited risk of cancer development.
Whole Genome and Whole Exome Sequencing. This will investigate at cohort level and look at variants enriched in those patients at the extreme of pain sensibility either high or low. Thus, since our cohort share pain perception as part of their phenotype, the risk of detecting variations in genes predisposing to e.g. cancer would be extremely low. We will use standardized analysis software to investigate variants e.g. common platforms such as ingenuity variant analysis.

The genes expected for sequencing is coding for ion channels (e.g. SCN9A, SCN10A, SCN11A, KCNS1), and enzymes (GCH1, COMT, FAAH), and trafficking proteins (CACNA2D1, NK1R). The biobank is a research biobank and all material will be destroyed at completion of the study. The analyses will be restricted to the neuropathy and neuropathic pain field. When the project and research biobank ends, all material will be destroyed. Patient who accepts biobank also accepts to be informed of incidental genetic findings with health impact unless they specifically declines (See the informed content).
Patients can participate in the clinical study independent of whether they accept to have a blood sample taken and stored in a research biobank or not. If they do not wish to have their blood stored in a biobank, they sign the informed consent S2[1]. If they accept to have their blood taken and stored in a research biobank, they sign the informed consent S4[2].

[1] *Standardsamtykkeerklæring udarbejdet af Det Videnskabsetiske Komitésystem, december 2011.*
[2] *Standardsamtykkeerklæring udarbejdet af Det Videnskabsetiske Komitésystem, december 2011 (Biologisk materiale)*

Data analysis, statistics, and number of patients.

This is a follow-up of an on going study and thus a new sample size calculation is not performed. We expect that around 30 patients in each treatment group will participate in the clinical study. Analysis will be mainly descriptive. In relation to performing single nucleotide polymorphism analysis to study the risk of developing pain, previous studies would predict a requirement of 200 patients per group as an estimate (however this depends on the strength of the genetic influence). For genome wide association studies very large group sizes (at least a thousand) are needed and data will be combined within the DOLORisk consortium.

Analysis of Quantitative Sensory Testing data will be in accordance with the DFNS protocol using Z-transferred data. Normality is tested using qq-plots. Data are analysed depending on the distribution using either unpaired t-test or Mann Whitney *U* test. The results will be presented as means ±SD if normal distributed and medians with 10 and 90 percentiles or range if not. Estimates are given with exact 95% confidence intervals. *P*- values < 0.05 will be considered statistically significant.

Data storing and transfer

The acquired data is stored on a personal computer that is password protected. The patient data is held in the local database at Aarhus University. Pseudonymized patient data will be transferred to participating centres in the DOLORisk consortium with the patient's consent, maintaining patient confidentiality at all times. Data transferred is answers of questionnaires and results of examinations. Anonymized data may also be made available to researchers outside the DOLORisk consortium as part of the ICMJE, International Committee of Medical Journal Editors, recommendations on data sharing. Thus, this informed consent also includes consent to a further use of the anonymous date for scientific use. A unique patient identification number is used for export of the data which is generated in the local center, so that export can be conducted without any personal data like the name, date of birth, residence.

The research group and practical framework

This study has been planned as a PhD project for MD Kristine Jepsen Bennedsgaard. Associate Professor Nanna Brix Finnerup, Danish Pain Research Center will be the main supervisor. Lise Ventzel, MD, PhD, Department of Oncology and Hatice Tankisi, MD, PhD, Department of Clinical Neurophysiology, will be co-supervisors. Head of Department, MD, PhD Anni Ravnsbæk Jensen, Department of Oncology, will be another collaborator. Lise Ventzel has conducted a prospective PhD study titled "Neuropathy and Pain after Chemotheraphy" with the same research group, from which the patients can be recruited for the PhD project. Other participants from the DOLORisk consortium are collaborators on parts of the study, including David Bennett, UK, Jordi Serra, Spain, and Geert Crombez, Belgium.

Feasibility, research education and time schedule

All examinations including QSTs, NCSs and threshold tracking are used for clinical and research purposes at the Danish Pain Research Center and the Department of Clinical Neurophysiology, Aarhus University Hospital. Kristine Jepsen Bennedsgaard will under supervision and after complete training, perform the neurological examination, Treshold Tracking, QST, and NCSs and be responsible for the examination of patients and control subjects. A trained research nurse at the Danish Pain Research Center will perform the CCM.

Time schedule: The first patients will receive the questionnaire in January 2016, and if there is no response a notification will be send 14 days later. The clinical examinations will take place from February 2016 until December 2019.

Publication and Dissemination

We expect to publish at least 1 scientific peer-reviewed paper in an international journal. Both negative, inconclusive and positive results will be tried to be published. Kristine Jepsen Bennedsgaard will be first author of the main publication. Relevant collaborators will be co-authors. DOLORisk (EU Horizon 2020) and Aarhus University will be acknowledged for their support. Further publications from this material, including the genetic results, will be published with relevant researchers in the DOLORisk consortium. Details regarding this issue have already been settled in the contracts with the DOLORisk participants

Economical Aspects

The study is mainly supported by the EU, grant number 633491 (Ph.D. scholarship, equipment purchase, etc. about 250.000 DDK) and Aarhus University (Ph.D. scholarship, about 100.000 DDK). The initiative to the study was taken by the sponsor in collaboration with the collaborators. The project participants do not have any connection to those supporting the study. There are no current plans of applying for more financial support to the project.
The project patients will not be paid. The transport will be paid according to the usual rules by the department.

Ethical Aspects

Risks, side effects and benefits:

The project requires participation in a series of examinations, which are mostly standard procedures at the involved departments and are conducted by experienced staff. In general the examinations are without risks. The electrophysiological procedures may cause slight discomfort due to the use of electrical stimulation. During thermal stimulation the minimal stimulation temperature is 0 °C and maximum stimulation temperature 50 °C. All thresholds during stimulation are reached with temperature changes of 1 °C/s. This technique does not provide tissue damage, and patients switch of stimulation themselves when pain threshold is reached. No known risks or side effects are observed in relation to the examinations. Patients with hypersensitivity can experience some of the stimulations as discomfort or painful. Patients can themselves at any time switch of the stimulation. Unknown side effects can occur.
Project participation will not influence the patient's possible medical treatment and the research subjects will be informed that they will not have direct personal benefits from the project participation. If the patient agrees to participant with a blood sample there are a small risk of very mild transitory pain, local hematoma, local irritation and minor local bleeding.

Subjects are covered by the public patient insurance, if any damage contrary to expectations is occurring during the examinations. Subjects will in case of damage or death not related to the project be covered by the hospital insurance.

Enlistment of the participants and guidelines for oral participation information

Patients who are participants in the on-going questionnaire survey are eligible. In the questionnaire, we ask if we may contact them with information on a clinical study and if so, we ask

them to provide their preferred contact details and preferred way of contact (mail, email or telephone) (see document "rekrutteringsmateriale"). After accepting contact regarding information about the clinical study, we will contact them via their preferred way of contact with a short information. If they are interested in more information, we will send them the written patient information and "Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt".
If they are still interested, they will be invited to a visit at the Danish Pain Research Center, where they will receive the oral information. The oral information meeting will take place in a closed office and there will be enough time to give information and discuss the possible questions. After the verbal information the patients will be offered at least 24 hours to decide, whether they want to attend to the project or not. The participants will also be informed that they can withdraw from the project at any time.

The participants' physical and mental integrity and private life's peace will be respected.

The project will be conducted in accordance with the Helsinki declaration II. The project is approved by the data protection agency (J.nr. 2011-41-5725), but we have sent in a new application to get approval to send pseudonymized data to other researchers, to send blood samples to the UK, and to register Kristine Jepsen Bennedsgaard as a the main investigator. The law on processing the personal information will be followed using REDCap

An informed written consent will be obtained from all patients before examinations. There are two different written consents one with acceptance of the study with blood sample(S4), and one with acceptance to participate in the study, without the blood sample (S2).

Handling of expected and unexpected/incidental findings:
It is not expected that we will find variants in genes that are linked to carcinogenesis or risk of disease. The study is performed in collaboration with Prof. Uffe Birk Jensen, Dept of Clinical Genetics, Aarhus University Hospital. He will appoint an independent committee in case of unexpected/incidental findings. This committee will evaluate whether there should be feedback to the patient and in this case provide counseling to the patient. This committee will also consider if report to relatives is recommended in case the patients is dead or do not want information on

own health. In addition, there will be possibility for the patient to receive genetic counseling before accepting to give blood to the biobank.

Overall it is judged that the expected gain of the project will exceed the disadvantages experienced by the research subjects, and that the project therefore is ethically justifiable. The conduction of the project will be of large importance regarding knowledge about chemotherapy induced neuropathy and pain Moreover, this project is expected to contribute to better understanding of pathophysiology of pain and eventually better treatment possibilities.

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