Maastricht University

Chemotherapy-induced peripheral neuropathy

Citation for published version (APA):

Peters - Beijers, T. (2016). *Chemotherapy-induced peripheral neuropathy: an underestimated side effect with major impact on quality of life*. [Doctoral Thesis, Maastricht University]. Ipskamp drukkers. https://doi.org/10.26481/dis.20161213tp

Document status and date:
Published: 01/01/2016

DOI:
10.26481/dis.20161213tp

Document Version:
Publisher's PDF, also known as Version of record

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy
If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Download date: 08 May. 2024

Valorisation

Introduction

It is essential for society that academic knowledge is translated into potential societal and economic benefit. This process is called valorisation and is precisely defined as *''The process of value creation from knowledge, by making it applicable and available for economic or societal utilization, and by translating it in the form of new business, products, services, or processes''*.[1] This chapter discusses the potential societal and economic value of the presented results of this thesis.

Cancer is diagnosed in about 100,000 patients each year in the Netherlands.[2] Systemic treatment like chemotherapy, is an important foundation in the management of many of these cancers. Treatment with cytostatics are accompanied with many adverse events, such as nausea, myelosuppression and peripheral neuropathy, which may have a major impact on patients' quality of life (QOL). In addition, those side effects could be the reason for the clinicians to decide to interrupt, modify or stop the treatment, which may lead to reduced chemotherapy efficacy and survival. Due to improved supportive management options for the adverse events chemotherapy-induced nausea and myelosuppression, chemotherapy-induced peripheral neuropathy (CIPN) has become one of the major dose limiting side effect of commonly used cytostatics.
Because of the increasing prevalence of cancer and the fact that there is still no proven preventive or treatment option for CIPN, more patients are confronted with the consequences of CIPN. Consequently, it is likely that CIPN will become a survivorship issue with major social and economic impact on society. Nevertheless, still many questions about CIPN remain unclear and therefore shedding more light onto the problem of CIPN and making patients and physicians more aware of this vital adverse event is of major importance for society. The results of this thesis have contributed to insight in many of those unanswered questions (Table 10.1).

Part I - Chemotherapy-induced peripheral neuropathy and quality of life

Until now the extent of CIPN remained unclear for society as the literature about the clinical manifestation and incidence of CIPN was very diverse due to the heterogeneity of studies and the use of different assessment methods. In addition, symptoms were most often reported by clinicians who are known to underreport CIPN and studies mainly focused on the short-term symptoms during treatment while the long-term consequences of reported symptoms and their impact on society remained unknown. The results in this thesis aid in increasing the knowledge about CIPN as we have

investigated which particular symptoms are most reported by different patient populations according to patient-reported outcomes, and which symptoms are most debilitating for them at the short- and long-term.
The included population-based studies confirmed that CIPN is a severe, unpredictable, and often irreversible adverse event of frequently used cytostatics, such as taxanes, oxaliplatin and antimyeloma treatment such as thalidomide and bortezomib. Patients reported mainly symptoms of tingling, numbness, pain and loss of strength in the hands and/or legs (chapter 2, 3, 4, 7). Those symptoms resulted in problems in e.g. fine motor skills, such as managing the computer, difficulty in writing or managing money, or problems in opening a bottle or climbing stairs due to loss of strength in hands or legs. We also clarified that many CRC survivors and patients with MM keep being confronted with the consequences of the neuropathy symptoms more than 10 years after diagnosis (chapter 3, 4, 7).
Before our research little was known about the influence of these symptoms on patients' functioning and QOL. We made clear that those symptoms not only influence their daily activities, but also have a major impact on their overall QOL (chapter 2, 3, 4). Patients who experienced the most severe symptoms of CIPN reported statistically and clinically relevant worse scores on all the domains of QOL including their physical, emotional and social functioning. With these findings we have elucidated that the social impact of CIPN is larger than expected and that the importance of awareness of this potentially severe side effect is vital for both patients and physicians.

Unfortunately, little is still known about the potential economic impact of the CIPN symptoms. Up to 30% of CRC survivors treated with oxaliplatin reported to experience severe CIPN symptoms two to 11 years after diagnosis (chapter 3) and more than half of patients with MM reported severe CIPN up to 13 years after diagnosis (chapter 4, 7). These patients are long-term cancer survivors and supposed to be reintegrated in society. However, it could be hypothesized that those patients are not able to work or economically contribute to society because of those symptoms. Moreover, guidelines recommend treatment with duloxetine, gabapentin, or pregabalin for chemotherapy-induced neuropathic pain.[3,4] Evidence concerning the effectivity of those drugs in case of neuropathic pain due to CIPN is however scarce.[3] Nonetheless, many patients are using these drugs in spite of lack of proven effectiveness which results in substantial costs for society. To my knowledge only one study has been performed which investigated the influence of CIPN on patients' workability[5], and none concerning healthcare usage and the resulting potential economic impact. Therefore, as our research indicates that long-term CIPN is more often reported than expected, a likely next step in research is to evaluate the potential economic impact of CIPN by evaluating healthcare usage or work disability because of CIPN.

Table 10.1 Societal contribution of the results presented within this thesis and future perspectives.

CIPN	What did we need to know?	Investigated within this thesis (chapter)	Contribution of knowledge to society presented within this thesis	Future perspectives for research
			Part I	
Pathophysiology	The precise mechanism underlying CIPN.	Not included	Not included	Discovering the underlying mechanisms of CIPN necessary to define potential targets for the prevention and treatment of CIPN.
Prevalence and clinical manifestation	Short- and long-term clinical manifestation and prevalence of CIPN in different patient populations	2, 3, 4, 7	Common dose limiting side effect: In patients treated with platinum derivatives and taxanes 6 months after treatment Up to 30% of CRC survivors treated with oxaliplatin experience severe CIPN symptoms 2 to 11 years after diagnosis. 53% of patients with MM reported severe neuropathy symptoms up to 13 years after diagnosis. Most reported symptoms: Tingling, numbness and pain in the hands and/or feet, loss of strength in the hands, erection problems for men	Assessment of prevalence and severity of CIPN with valid, uniform, patient-friendly and reliable measurement The measurement preferably van be used in daily care.
Influence of CIPN on QOL	Evidence is scarce. What is the influence of CIPN on patients' QOL?	2, 3, 4	CIPN has a negative influence on all the domains of daily functioning and QOL of CRC survivors and patients with MM.	Further research is warranted because of the diversity of the studied patient populations and differences in CIPN and QOL measurements Studies should determine not only statistically significant differences, but also report if these differences are clinically important to patients.

Table 10.1 (continued)

CIPN	What did we need to know?	Investigated within this thesis (chapter)	Contribution of knowledge to society presented within this thesis	Future perspectives for research
Diagnosis: Assessment tools	No consensus in diagnosis. What should a valid assessment tool incorporate?	4	Assessment tool should incorporate at least a patient-reported outcome. The self-reported ICPNQ may be a valuable tool which can be incorporated easily in clinical practice.	The development of a valid, uniform, patient-friendly and reliable measurement. Easy to use in daily clinical practice. It should incorporate at least a patient-reported outcome measurement to overcome underreporting by clinicians.
Influence sociodemographic and clinical factors on development of CIPN	What sociodemographic and clinical factors are relevant for the development of CIPN?	5, 6, 7	Oxaliplatin and thalidomide, and especially a higher received cumulative dose, was associated with the severity of neuropathy. CIPN was not associated with dose-intensity, age, sex, time since last course of therapy, number of prior therapies and comorbidity Dose was often modified because of CIPN in CRC and MM patients. Patients who received a dose modification because of CIPN still reported worse levels of CIPN at the long term	Identifying patients at risk of developing CIPN is of major importance in order to personalize cancer care e.g. sociodemographic, clinical and genetic variations.
Prevention	How can we prevent the development of CIPN?	6,7 General discussion	Modify dose on time	Pharmacological interventions to prevent/treat CIPN induced neuropathic pain/symptoms.
Treatment	How can we treat the symptoms of CIPN?	Not included General discussion		Non-pharmacological options e.g. frozen gloves, dietary supplements (e.g. ALC), rehabilitation.

ALC: acetyl-L-carnitine; CIPN: chemotherapy-induced peripheral neuropathy; CRC: colorectal cancer; ICPNQ: indication chemotherapy-induced peripheral neuropathy questionnaire; MM: multiple myeloma; QOL: quality of life.

Another issue, which has been debated and impeded the knowledge of the clinical manifestation of CIPN and its influence on QOL before, is the lack of a consensus on diagnostic assessment tools to measure CIPN.[6] Since clinicians tend to underestimate CIPN by using the common toxicity grading scales and objective measurements are not patient-friendly, expensive and do not correlate with subjective symptoms, the use of a self-reported questionnaire has been recommended.[3] In our studies, we therefore used self-reported questionnaires to evaluate CIPN. However, although highly needed, it should be mentioned that most assessment tools including questionnaires are not developed nor used in daily clinical practice at the moment. Therefore, in chapter 4 we also validated a self-reported measure (ICPNQ) which has been made to be applicable for daily clinical practice. The ICPNQ appeared to be a valid instrument to distinguish the higher grades of CIPN from the lower grades in a uniform way and overcomes the issue of underreporting CIPN by clinicians.

This questionnaire can be used in daily clinical practice since it is based on the common toxicity criteria which are used in current guidelines to decide on dose modifications. Further prospective evaluation of this questionnaire however is needed in order to evaluate the ability to monitor the development of CIPN over time, and to compare the self-reported neuropathy with physician reported neuropathy, and its use in decisions regarding dose modifications.

Part II - CIPN and the influence of chemotherapy administration

Currently, dose modification schemes are the only way to prevent moderate CIPN symptoms to become more severe. As CIPN potentially has a major societal and economic impact, it is of major importance for society to be able to identify patients at risk of developing CIPN on time, or preferably before the start of treatment. Accordingly, patients who are prone to develop CIPN can benefit from personalized medicine when deciding on the best therapy with the least toxicity. At the moment, patients with preexisting neuropathy who are more likely to develop CIPN are identified before treatment, but otherwise it is difficult to completely recognize patients who are prone to develop CIPN. There are signs that encoding genes are involved in the development of CIPN. However, since genomic studies are still in its infancy and not routinely used in usual care, for the time being it is important to identify sociodemographic and clinical characteristics involved in the development of CIPN. Within part II of this thesis, we investigated the influence of chemotherapy administration and dose modifications on the development of CIPN (chapter 5, 6, 7). These studies contribute to the knowledge about the development of persistent CIPN. Within these three chapters we reported that the dose was often modified because of

CIPN and that especially a higher received cumulative dose of oxaliplatin in CRC patients and thalidomide in patients with MM was an important risk factor for the development of long-term CIPN (chapter 5, 6, 7). CIPN was not associated with dose-intensity, age, sex, time since last course of therapy, number of prior therapies and comorbidity. The societal value lies in the fact that this emphasized that monitoring of CIPN during treatment is of major importance as dose might be modified on time. To do so, as mentioned earlier, a proper assessment tool which can be used in daily care is essential. The questionnaire presented in chapter 4 might be a valuable tool for this purpose.
Furthermore, cancer response rates were described to be the same between patients who received or did not receive a dose modification because of CIPN (chapter 6,7). Nonetheless, study design and sample sizes of our studies were not intended to investigate this question. However, it would be of great interest to investigate if dose modifications could be safely applied at lower levels of CIPN without compromising response rates. If this is possible, patients will experience lower levels of CIPN at the long-term with societal benefit. In addition, also economically this would be of value as the costs of chemotherapy and symptom-alleviating drugs could be lowered. Moreover, as patients have lower levels of CIPN they might be able to live longer independently without extra care.

In conclusion, the main value for society of the presented studies in this thesis are numerous as still many questions about this common, frequently dose limiting and debilitating side effect are unanswered. This thesis sheds more light on the problem of CIPN and emphasizes that CIPN has a major societal impact as many patients suffer from difficulties in daily activities and have a worse QOL because of CIPN. Furthermore, CIPN has a major hypothesized economic impact on the society which should be further investigated. As some patients are likely to be more prone to develop CIPN, personalized medicine should be more integrated to prevent patients and society from the burden of this devastating side effect. For the near future especially the usage of a valid assessment tool to measure CIPN in a reliable way is important. This is not only important for proper monitoring CIPN during treatment, but also highly needed for suitable research concerning al the aspects of CIPN which are still unanswered.

References

1. Regulations governing the attainment of doctoral degrees. Maastricht University 2013:51.
2. http://www.cijfersoverkanker.nl/incidentie-sterfte-50.html (Accessed on 15 July, 2016).
3. Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G et al. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2014;32:1941-1967.
4. van den Beuken-van Everdingen MH, de Graeff A, Jongen JL, Dijkstra D, Mostovaya I, Vissers KC, et al. Pharmacological Treatment of Pain in Cancer Patients: The Role of Adjuvant Analgesics, a Systematic Review. Pain Pract. 2016.
5. Zanville NR, Nudelman KN, Smith DJ, Von Ah D, McDonald BC, Champion VL, et al. Evaluating the impact of chemotherapy-induced peripheral neuropathy symptoms (CIPN-sx) on perceived ability to work in breast cancer survivors during the first year post-treatment. Support Care Cancer. 2016 Jul 28.
6. Cavaletti G, Frigeni B, Lanzani F, Mattavelli L, Susani E, Alberti P, et al. Chemotherapy-Induced Peripheral Neurotoxicity assessment: a critical revision of the currently available tools. Eur J Cancer. 2010 Feb;46(3):479-494.