Peripheral Neurotoxicity Induced by Taxanes, Cisplatin, Oxaliplatin, Fluoropyrimidines and Vinorelbine

A clinical perspective

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Chemotherapy-induced peripheral neuropathy (CIPN) is the type of toxicity that affects treatment decisions often. Oncology specialists usually grade it using Common Terminology Criteria for Adverse Effects version (CTCAE), with some limitations. Dyck scale is a more objective method that is usually used for diabetic neuropathy grading.The present study included retrospectively registered patients (n=80) treated with platinum salts, taxanes, fluoropyrimidines or vinorelbine that subsequently developed CIPN. In some, the decision to lower the chemotherapy dose or withhold the treatment altogether was taken. CIPN was graded using both CTCAE 4.0 and Dyck scale for each patient. The aim of the study was to determine how the grades of each scale influenced the decision on the oncological treatment and whether objective, measurable changes are directly proportional to the impact CIPN has on the patients life. The present study reports high sensibility for both CTCAE and Dyck scale in deciding to modify the dose or interrupt chemotherapy. CTCAE should have more importance for the clinician in the early stages of CIPN. If CIPN presents as advanced, a less subjective alternative like the Dyck scale is a more suitable alternative. Dyck scale should be the most important argument in the decision regarding oncological treatment if the patients' scores more than 2a on this grading system.The decision to lower the dosage or stop oncological treatment due to CIPN is a complex one and both grading systems are useful. However, when dealing with a more severe case of CIPN, the more objective Dyck scale should be the more important argument.

Keywords:neurotoxicity, chemotherapy, grading

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Chemotherapy-induced peripheral neuropathy (CIPN) is the type of toxicity that affects treatment decisions often. Several limitations in its' grading have been reported. Classification usually includes a mixture of objective and subjective parameters. No matter what scale one uses the difference between grade 1 and grade 4 is not difficult to asses for either the treating oncologist, nor the neurologist. But what about the difference between grade 2 and 3? One has to take in consideration that grade 3 usually implies chemotherapy dosage modification and an active intervention in an efficient oncological treatment. Whether the subjective criteria or the objective ones matter most is a pending question. The patient's occupation is an important issue to be taken into consideration. Do fingertip paresthesias mean the same to a pianist than anyone else? Is sensory loss in the feet the same for a driver than for a person that does not drive? Objective neuropathy criteria are the ones that appear early and may enable clinicians to act more promptly. These first signs may enable treatment that slows down the toxicity evolution. On the other hand, over grading this toxicity may lead to early chemotherapy dosage lowering, which can impact the patients' outcome. The choice of the scale by which we grade this toxicity is a complex one.

Experimental part

Methods

The present is a retrospective, observational pilot study that focused on determining whether grading chemotherapy-induced neuropathy using the Dyck scale has the same impact on oncological treatment decision as grading with Common Terminology Criteria for Adverse Effects version 4.0 (CTCAE). In addition, we aimed to determine whether high grades on each scale were correlated with the decision to lower the dose or discontinue treatment.

A number of 80 patients with various cancer types (*N=80*) were included in the study, all of which had received chemotherapy with taxanes, cisplatin, oxaliplatin, fluoropyrimidines and vinorelbine and were diagnosed with chemotherapy-induced peripheral neuropathy, mostly sensory or motor, but a few had autonomous neuropathy. The study included all the patients that fit these characteristics and had been treated between 2015 and 2016.Data analysis was performed using GraphPad 6 Prism 2017 and MedCalc 14 for Windows 7. Patients were included in the study if they had received only one type of each agent described above.History of combination chemotherapy with agents that are not reported to induce CIPN was permitted. Demographic factors such as age,

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sex and living area were acquired. We excluded from the study patients with diabetes mellitus, or any other conditions other than chemotherapy that can be related to peripheral neuropathy. Clinical factors like the number of chemotherapy courses, time to neuropathy diagnosis and peripheral neuropathy distribution were recorded.

The neurologic evaluation was performed based on clinical (Dyck scale) and electrophysiologic examinations. Investigating patients with CIPN this way was at the time institutional procedure. The Dyck scale allows a complex and objective evaluation of the peripheric neuropathy. It is an easy to use tool for a neurologist, the average duration being of about 10-15 min and it is less influenced by the subjective answers of the patient. However, it requires a neurology specialist in order to have a proper evaluation. It consists of 2 subscores, the first determining the the presence of neurological symptoms and the second focusing on the severity of the symptoms. Each symptom is evaluated bilaterally and graded (0-4). A high score translates into a more significant clinical impairment, the score associating a high sensitivity level. Electrophysiologic tests were performed in the Neurology Department according to the local protocol, using specialized equipment (Nicolet Viking IV P NCS, Electromyography, EP system). Sensory Nerve Conduction studies (median, ulnar, sural and superficial peroneal nerves), Motor Nerve Conduction Studies (median, ulnar, peroneal and tibial nerves), F and H waves were measured. Results were graded using Dyck scale, which combines electrophysiologic studies and clinical testing and does not include subjective grading elements (table 1). The same patients' symptoms were also graded by the treating oncologist using the CTCAE (table 1). The aim was to determine whether great discrepancies existed between the two scales in the studied patients. The decision to lower the chemotherapy dose was taken analyzing both scales for each case.

Results and discussions

Patients characteristics

Among the 80 patients that were included in the study mean age was 59.12 (SD=11.03), 42.5% percent were men and 57.5% percent were women. Most of the patients lived in the urban area (59.3%). Most were treated for gastrointestinal malignancies (n=32, 39.5%) followed by gynecological ones (n=13, 16.3%) and non small cell pulmonary cancer (n=13, 16.3%). Mean time since first chemotherapy administration and the diagnosis of peripheral neuropathy was 3.43 months (SD=1.86). Maximum duration of first chemotherapy course to neuropathy diagnosis was 8 months, and minimum duration was 1 month. Types of chemotherapy mostly used were as follows (table 2): taxans+combination (n=28, 34.6%), followed by cisplatin+combination (n=21, 25.9%) and oxaliplatin+combination (n=21, 25.9%). Out of all the patients 14.8% (n=12) also received bevacizumab. A small number of the patients with autonomous neuropathy or radiculopathy (n=7) were excluded from the analysis, being unclassifiable by Dyck scale.

When using CTCAE, most patients were assessed as: asymptomatic; clinical or diagnostic observations only-grade 1 (39.5%), followed by grade 2: moderate symptoms; limiting instrumental activities of daily living (34.6%). The same patients were assessed by Dyck scale and most of them were classified with grade 2a peripheral neuropathy – neuronal conduction of stage 1a with or without signs (but if present lower than 2b) and with typical neuropathic symptoms (59.3%), followed by the highest grade – grade 2b- neuronal conduction abnormality of stage 1a, a moderate degree of weakness (i.e., 50%) of ankle dorsiflexion with or without neuropathy symptoms (14.8%).

Statistical analysis

To verify if the decision to reduce chemotherapy dose or to stop treatment was associated with high values of the CTCAE score, the sample was divided into 2 parts. T test for independent variables wasused to check for differences (fig. 1).

As figure 2 illustrates, CTCAE grade is higher in patients whose therapy was reduced or stopped in comparison to the ones with no treatment change (2.714 ± 0.5527, n=21 vs. 1.500 ± 0.1079 *N=58*, 95%CI= -1.961 to -0.4679,*p=0.0018*).

The same was done for Dyck scale and the results are illustrated in Figure 3 and Figure 4.

As in the previous analysis, the group of patients in which the dose was reduced or the therapy was stopped, the Dyck scale values were higher with statistical significance

Scale				
CTCAE 4.04	Grade 1	Grade 2	Grade 3	Grade 4
	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL*	Severe symptoms; limiting self care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated
Dyck scale	Grade 1a	Grade1b	Grade 2a	Grade 2b
	abnormality of NC, e.g., 5 NC normal deviates>95th percentile without symptoms or signs	NC abnormality of stage 1a plus neurologic signs typical of DSPN but without neuropathy symptoms	NC abnormality of stage 1a with or without signs (but if present<2b) and with typical neuropathic symptoms	NC abnormality of stage 1a, a moderate degree of weakness (i.e., 50%) of ankle dorsiflexion with or without neuropathy symptoms

*ADL=activities of daily living

Table 1
GRADING SCALES USED FOR CIPN[1,2]

Table 2

PATIENTS' CHARACTERISTICS

Number of patients	80
Sex	
Female	46
Male	34
Age (in years)	
Range	31-82
Median	59.12
Cancer site	
Gastro-intestinal	32
Genito-urinary	5
Breast	12
Gynecological	13
Melanoma	1
NSCLC**	13
Head and Neck	4
Time to CIPN (in months)	
Range	1-8
Median	3.43
Type of chemotherapy	
Taxans+/-combination	28
Cisplatin+/-combination	21
Oxaliplatin+/-combination	21
Fluoropyrimidine+/-combination	9
Vinorelbine+/-combination	1

**NSCLC=non small cell lung cancer

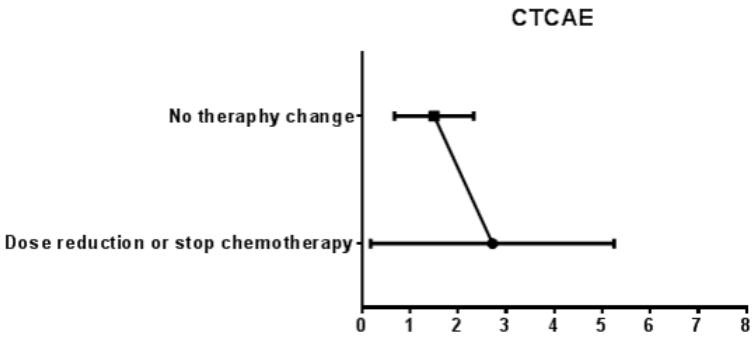

Fig. 1. Independent variables in the decision to reduce chemotherapy dose or to stop treatmentin relation to CTCAE score.

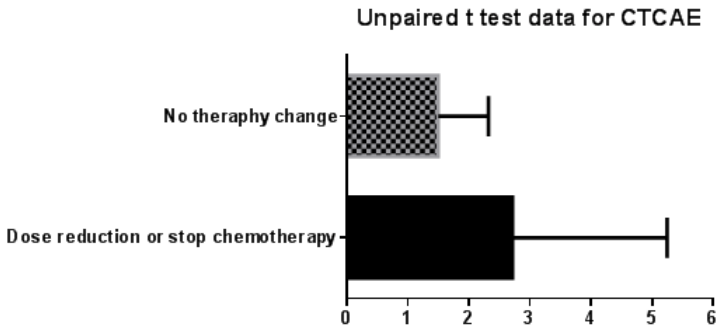

Fig. 2. T test for independent variables in the decision to reduce chemotherapy dose or to stop treatment for values of the CTCAE score.

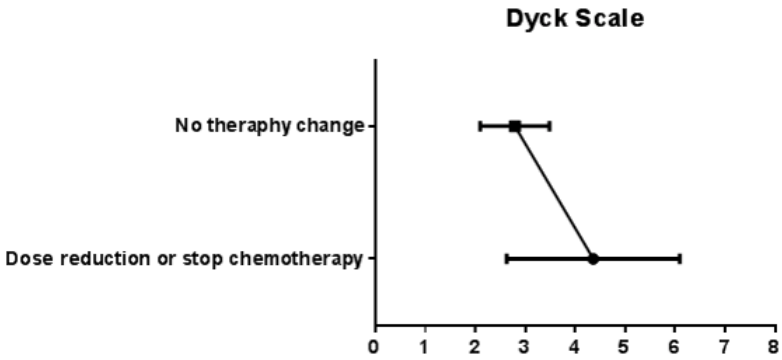

Fig. 3.Independent variables in the decision to reduce chemotherapy dose or to stop treatment in relation to Dyck scale.

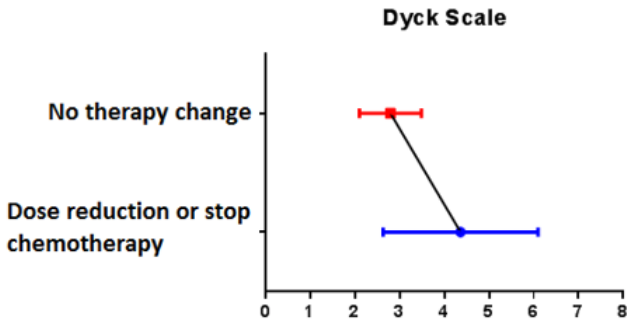

Fig. 4.T test for independent variables in the decision to reduce chemotherapy dose or to stop treatment for values of Dyck scale.

(4.364 ± 0.3695 *N=22* vs 2.793 ± 0.09123 *N=58*, .95%CI=-2.108 to -1.033, $p<0.0001$). Moreover, we hypothesised the Dyck scale to be a more valuable tool than CTCAE when deciding to modify treatment due to peripheral neuropathy. To demonstrate this ROC curves were analyzed. Variables in the curves were the CTCAE and Dyck scores and the classifying criterion was the decision to modify treatment. Graphic representation can be seen in figure 5 and 6.

CTCAE score proved efficient in guiding the decision to maintain treatment. Although the specificity was low (12.1%) we can state that a patient with CTCAE score equal or less than 2 can continue with previous chemotherapy.

The ROC curve for Dyck scale proved the test efficiency in deciding to reduce the dose or discontinue treatment. It has acceptable sensibility (42.7%) and excellent specificity (91.4%) if the score is equal or higher than 2a (criterion >3).

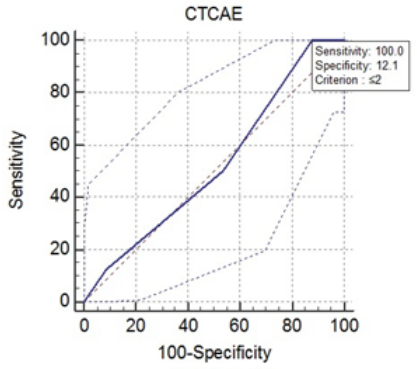

Fig. 5. ROC curve (sensibility and specificity of CTCAE in treatment decision making)

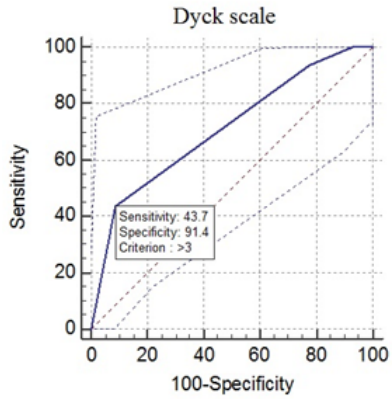

Fig. 6.ROC curve (sensibility and specificity of Dyck Scale in treatment decision making)

Even if both scores proved their efficiency, pairwise comparison of both curves is essential, as represented in figure 7. The area under the curve (AUC) is larger for the Dyck scale (0.712 vs. 0.525 for CTCAE), this being proof that Dyck scale is more relevant in the decision to modify treatment. Even so, the difference between the two areas has low statistical significance (*p=0.073*).

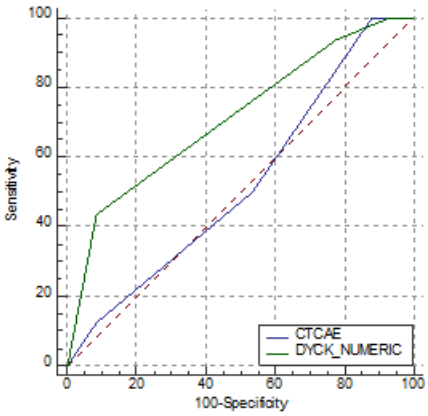

Fig.7. Comparison of specificity and sensibility in treatment decision making when using CTCAE vs. Dyck Scale

To establish whether any correlation exists between the two scales we used Pearson/Spearman coefficient. We concluded that they are in close correlation, their values rising directly proportional (r=0.7602, 95%, CI= 0.65-0.84, *p<0.0001*).

We also analyzed the relationship between the period from diagnosis (in months) and both scores. CTCAE grade seems to be higher as more time passes from the diagnosis (positive r, r=0.2286, 95%CI= 0.007-0.42, *p=0.042*).

When analysing the same for Dyck scale, positive correlation resulted between the duration and the grades of the scale, but with no statistical significance (r=1504, 95% CI=0.071-0.35, *p=0.81*).

A general percentage of 30-40% of all patients who receive chemotherapy will eventually develop some type of CIPN [3,4].

Up to date, there is no consensus on which is the most important aspect of peripheral neuropathy: quantitative sensory abnormalities or subjective functional impairment in daily life activities. Several scales are available to grade CIPN like WHO, CTC, Ajani and ECOG (Eastern Cooperative Oncology Group) [5].

Dyck scale emerged as a quantitative measure of diabetic peripheral neuropathy. It sums up signs, symptoms and most important abnormalities in nerve conduction (NC). NC testing is an important aspect for the objective evaluation of peripheral neuropathy, but it cannot be put in context without also reporting signs and symptoms. Diabetic neuropathy is thought to result from microvascular injury and from the accumulation of glycated end products within the cells. CIPN, however, has a complex physiopathological mechanism, typical for each agent. These differences are the first rebuttal argument when deciding to use Dyck scale for grading neuropathy. Even so, one has to take in consideration that regardless of the principal mechanism in both situations the result is neuronal apoptosis and in both cases, long fibers are affected to a greater extent than the shorter ones, so significant similarities exist [6-8]

When reporting signs and symptoms, the patients' perception of the degree of impairment is also influenced by the other toxicities. Patients suffering from nausea or pain complain of higher neurological impairment[9].

Differential diagnosis between diabetic neuropathy usually presents as distal symmetrical polyneuropathy or as mono neuritis multiplex, making it very difficult to differentiate from CIPN. This is why any patients suffering from diabetes were excluded from our study.

Different chemotherapy agents come with the various mechanisms of neurotoxicity like: changes in neuronal excitability, vascular cell apoptosis, and ischemia, axon degeneration, calcium homeostasis, or oxidative stress (table 3). Platinum analogs bind to the two DNA strands and modify its tertiary structure. Intracellular signaling pathways are then activated (usually implying D1-cyclin) that force the neuron into reentering the cell cycle, but this process leads to apoptosis in a differentiated cell. Oxidative stress is one of the most important mechanisms of cell damage of cisplatin. It leads to membrane lipid peroxidation and neuronal apoptosis. Oxaliplatin, however, has a different neurotoxic mechanism: the oxalate that results from its metabolism chelates intravenous calcium. This prevents the natrium channels in the neuron to correctly depolarize and changes in neuronal excitability result.

Taxanes prevent micro-tubules depolymerisation, which is involved in the cellular cycle, but also in the elementary functions of differentiated cells like the neuron. Disrupting these functions leads to axonal degeneration, which is usually irreversible.

Induction of apoptosis in endothelial cells is also described for both taxanes and platinum analogs. Apoptosis leads to vasa nervorum compromise and neuronal ischemia,which leads to neuronal loss[14-17].

Fluoropyrimidine associated CIPN is considered to be a rare event. Reports of it in the literature include case reports and clinical trials with few patients. For example, one of the most cited trials on the matter is one that included 28 patients receiving radiotherapy concomitant capecitabine, out of which, only 2 reported symptoms associated with CIPN and only in one case dosage modification was necessary[14].

Moreover, there seems to be a difference in CIPN associated with 5-FU versus the one associated with capecitabine. Several allegations of 5-FU associated peripheral neuropathy usually with 24-46h infusion regimens are present in the literature[18].

Table 3
ANTINEOPLASTIC AGENTS USED IN THE STUDY AND THEIR CHARACTERISTICS [10-13]

Agent	Mechanism of CIPN	Incidence	Clinical manifestions	Evolution
Cisplatin	Neuronal apoptosis	30-40%	Pure sensory neuropathy	Irreversible
Oxaliplatin	Neuronal apoptosis	50-60%	Distal or perioral paresthesias or dysesthesias	40% full recovery
Paclitaxel	Disfunction of axonal transport mediated by microtubules	70-95%	Sensory-motor neuropathy	Reversible in most patients
Docetaxel	Disfunction of axonal transport mediated by microtubules	50%	Sensory-motor neuropathy	Reversible in most patients
Fluoropyrimidines	None described			
Vinorelbine	Disfunction of axonal transport mediated by microtubules	20-30%	Sensory-motor neuropathy	Reversible

Capecitabine induced neuropathy seems to be caused by metabolites like fluoro-beta-alanine or 5-FU itself, which result after liver metabolism. Hand-foot syndrome, one of the most frequent and important adverse effect of capecitabine, consisting of paresthesia, dysesthesia, pain and intolerance to extreme temperatures, together with palmar and plantar skin changes seems to be related to nerve damage as well. Epidermal small fiber density is reported to be significantly lower in the affected population than in the normal one. This theory has to be confirmed in larger population studies[19, 20].

Treatment strategies

Efforts have been made to develop both prevention and treatment options for CIPN. Antioxidants like glutathione or glutamine can be considered for prophylaxis because they can protect the neuronal cell body from toxic accumulation or DNA damage. N-acetylcysteine has been used together with oxaliplatin with some benefit. Phase 2 clinical trials on the effect of adding vitamin E to cisplatin and paclitaxel proved efficacy in lowering the CIPN incidence. The benefit was not confirmed by phase 3 clinical trials[21-23].

Because of the particular mechanism of oxaliplatin to produce CIPN, which was previously described, Ca and Mg infusion was a logical solution. One study reported neurotoxicity incidence lowering and higher reversibility of CIPN with this approach. Even more, the antineoplastic efficacy of oxaliplatin was not affected [25,26].

Antiepileptic and antidepressant drugs are well-known options in neuropathic pain. They have been used with limited efficacy in CIPN as well. Trials used valproate, venlafaxine and oxcarbazepine. Venlafaxine proved to be the most efficient both in acute symptoms and in the prevention of severe chronic CIPN. However, this option comes with its' toxicity as well[27-29].

Particularities of our study consist in choosing the decision to modify or cease treatment due to CIPN, whereas most studies on this matter focus on the presence or absence of neuropathy. It also focuses on Dyck scale, which is rarely used for grading CIPN. Even so, decision of dose reduction or cesation of treatment was taken individually for each patient, taking in consideration his/her needs, wishes and the individual situation.

Our study reports high sensibility for both CTCAE and Dyck scale in deciding to modify the dose or interrupt chemotherapy. However, we have to acknowledge that CTCAE has very little sensibility. This is consistent with data in the literature [30]. If we take the present data in consideration, CTCAE should have more importance for the clinician in the early stages of CIPN. If CIPN presents as advanced, a less subjective alternative like the Dyck scale should also be used together with CTCAE. Our research suggests that Dyck scale should be the most important argument in the decision regarding oncological treatment if the patients' scores more than 2a on this grading system. The only scale that correlates with the period since diagnosis and has statistical significance is CTCAE. This is probably because of its' subjective nature. When comparing the two scales, the Dyck measurement system proved more relevant, but interestingly, the difference between the two was not statistically significant. Therefore, in any decision, both scales have their part.

Although efforts to develop new and more efficient treatment strategies of CIPN are constant, the most efficient option remains the lowering or interruption of chemotherapy. Because of its' high incidence and meaningful impact on patients quality of life, CIPN is the reason why some classical protocols of treatment are revised. Recently, three months of oxaliplatin-containing adjuvant treatment in a particular group of colorectal cancer patients instead of six months were proposed, in order to lower the incidence and impact of CIPN in this category of patients [30]. The possibility to deliver the same dose of chemotherapy in a more targeted fashion, using drug-loaded liposomes has been studied recently in vitro, with optimistic results. It has been demonstrated that the antitumor effect of oxaliplatin administered this way is present. Whether neurotoxicity incidence and grade can

be reduced by this type of administration is still a matter of debate [31,32].

To conclude, our data indicate that the decision to lower the dosage or stop oncological treatment due to CIPN is a complex one and both grading systems are useful. However, when dealing with a more severe case of CIPN, Dyck scale should make an important argument in any decision.

Conclusions

Being one of the most durable toxicities in oncological treatment, CIPN deserves special attention. New grading scales and more complex evaluation tools are useful for the right treatment decision. Larger clinical trials are needed to determine which is the best grading option or whether more than one.

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