Annals of Oncology **11**: 509–513, 2000.

Review

Grading of chemotherapy-induced peripheral neuropathy

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Key words: assessment, chemotherapy, peripheral neuropathy

Introduction

Peripheral neuropathy can be defined as a derangement in structure and function of peripheral motor, sensory, and autonomic neurons [1], causing peripheral neuropathic symptoms and signs.

In routine clinical practice settings, neuropathic symptoms are evaluated by a more or less standardized neurological history taking. Assessment of neuropathic signs is usually performed with bed-side clinical examination (sensory and motor abnormalities, reflex loss, orthostatic hypotension, etc.) or with quantitative methods such as nerve conduction studies, electromyography, and quantitative sensory threshold determination [2].

Peripheral neuropathy is observed frequently in patients treated with neurotoxic chemotherapeutic agents, including cisplatin, vincristine, and paclitaxel [3]. Vincristine and paclitaxel-induced neuropathy tend to occur early during therapy, with amelioration after discontinuation of therapy, whereas cisplatin-induced neuropathy tends to develop only after a certain cumulative dose level, and frequently worsens during the first months after therapy discontinuation [4]. Chronic peripheral neuropathy is a fairly common observed phenomenon, especially with cisplatin, and may lead to substantial negative impact on quality of life [5].

Chemotherapy-induced peripheral neuropathy is usually related to cumulative dose or dose-intensity, and with the advent of bone marrow stimulants like granulocyte colony-stimulating factor, precluding dose-limiting bone marrow toxicity, higher chemotherapy doses are used [6]. The development of regimens combining neurotoxic chemotherapeutic agents (e.g., cisplatin and paclitaxel) may also induce more pronounced or even dose-limiting peripheral neurotoxicity [7], necessitating reliable assessment of chemotherapy-induced peripheral neurotoxicity. This is certainly mandatory when the effects of potential neuroprotective agents are to be studied. However, the assessment of the severity of chemotherapy-induced neuropathy is difficult.

This review article will discuss the various ways of assessing chemotherapy-induced peripheral neuropathy, and will emphasize the need for reliable grading of severity of this toxicity, including a quality of life estimate.

Grading systems of chemotherapy-induced toxicity

To improve accurate and reliable reporting of chemotherapy-induced toxicities, several comprehensive toxicity grading systems have been developed [8–11]. The peripheral neuropathy sections of these systems differ from one to the other, but they all use a combination of 'subjective' and 'objective' parameters, e.g., moderate or severe paresthesias and reflex loss, respectively (see Table 1). One may question, however, whether clinical neurological signs (the doctor's perspective) are objective and important enough for accurate neuropathy grading. The examination of deep tendon reflexes, sensory modalities and motor function are all dependent on the cooperation of the patient and, as such, not entirely objective. Intra and interobserver variability in the estimation of reflexes, and motor or sensory disturbances play a role as well [12]. Moreover, physician-based common toxicity grading systems can be interpreted differently by observers [13, 14], leading to varying estimates of the incidence and severity of chemotherapy-induced toxicity. This difference will certainly be true with various toxicity rating systems used by separate research groups in multicentre trials when both medical oncologists and neurologists are involved. Clear guidelines how to use these toxicity grading systems are lacking. Another problem with the currently used chemotherapy-induced (neuro)toxicity rating scales is, that changes from baseline symptoms and signs, and chronic toxicity (which often occurs in chemotherapy-induced peripheral neurotoxicity) are poorly dealt with.

Quantitative assessment of chemotherapy-induced peripheral neuropathy

Most medical oncology articles regarding chemotherapy-related neurotoxicity use toxicity severity rating scales

Table 1. Grading scales for chemotherapy-induced peripheral neuropathy.

Scale	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
WHO [8]	None	Paresthesias and/or decreased tendon reflexes	Severe paresthesias and/or mild weakness	Intolerable paresthesias and/or marked motor loss	Paralysis
ECOG [9]	None	Decreased deep tendon reflexes, mild paresthesias, mild constipation	Absent deep tendon reflexes, severe paresthesias, severe constipation, mild weakness	Disabling sensory loss, severe peripheral neuropathic pain, obstipation, severe weakness, bladder dysfunction	Respiratory dysfunction secondary to weakness, obstipation requiring surgery, paralysis confining patient to bed/wheelchair
NCIC-CTC [11]					
Neurosensory	None or no change	Mild paresthesias, loss of deep tendon reflexes	Mild or moderate objective sensory loss, moderate paresthesias	Severe objective sensory loss or paresthesias that interfere with function	–
Neuromotor	None or no change	Subjective weakness, no objective findings	Mild objective weakness but no significant impairment of function	Objective weakness with impairment of function	Paralysis
NCIC-CTC (revised version 1999)					
Neuropathy-sensory	Normal	Loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Objective sensory loss or paresthesia (including tingling) interfering with function, but not interfering with activities of daily living	Sensory loss or paresthesia interfering with activities of daily living	Permanent sensory loss that interferes with function
Neuropathy-motor	Normal	Subjective weakness but no objective findings	Mild objective weakness interfering with function, but not interfering with activities of daily living	Objective weakness interfering with activities of daily living	Paralysis
Ajani [10]					
Sensory	None	Paresthesia, decreased deep tendon reflexes	Mild objective abnormality, absence of deep tendon reflexes, mild to moderate functional abnormality	Severe paresthesia, moderate objective abnormality, severe functional abnormality	Complete sensory loss, loss of function
Motor		Mild or transient muscle weakness	Persistent moderate weakness but ambulatory	Unable to ambulate	Complete paralysis

such as the WHO or CTC criteria, or single-institution classifying systems in which quantitative assessments like vibration perception threshold (VPT) measurements or nerve conduction velocity studies are frequently included [15–21].

In neurology literature on diabetic peripheral neuropathy, several neuropathic symptoms and signs scales have been developed, such as the Neurological Symptom Score, the extensive Neuropathy Symptom Profile, and the Neurological Disability Score [22, 23]. These physician-based scales are used primarily in diabetic neuropathy trials in order to diagnose the absence or presence of peripheral neuropathy, while the Neurological Symptom Score does not emphasize severity of complaints. Furthermore, consensus guidelines have been published on quantitative sensory testing [24], and on standardized measures in diabetic neuropathy [25]. However, there are pitfalls in quantitative sensory testing [26].

In neuro-oncological literature, most authors use combinations of a clinical description of peripheral neuropathic symptoms and signs supplemented by some form of quantitative assessment, such as VPT, or thermal discrimination threshold (TDT) measurements, nerve conduction velocity studies, or even sural nerve biopsy [7, 27–34]. Quantitative nerve function assessments and histological nerve examination can give valuable information on etiology (demyelinating or axonal, large-fiber or small-fiber abnormalities, neuronopathy or axonopathy, etc.), and extent of peripheral nerve involvement (subclinical abnormalities, focal or wide-spread nerve dysfunction, etc.). However, quantitative test abnormalities frequently coincide with clinical symtoms and signs, and are not necessarily informative in addition to the clinical impression [16, 27, 34]. Furthermore, the clinical severity is not necessarily reflected by quantitative test abnormalities. Besides, nerve conduction velocity studies, electromyograms and, especially, sural nerve biopsy are not without discomfort for the patient.

Quality of life assessment

One may argue that subjective parameters are at least as important as objective parameters in grading of chemotherapy-induced neuropathy. Paresthesias, pain or impairment of function may interfere severely with quality of life (the patient's perspective) and may be, in that respect, more relevant than absent reflexes or elevated sensory detection thresholds. Furthermore, neuropathic symptoms and signs may be judged by the patient to be not as important, or not interfering with quality of life, in the setting of potential curative chemotherapy.

In other words: who scores the severity of paresthesias or the extent of functional abnormality? Who judges the severity of chemotherapy-induced peripheral neuropathy? The doctor or the patient? The doctor may assess the degree of sensory abnormality or muscle weakness, but it is the patient who experiences a handicap in daily life and the impact of peripheral neurotoxic symptoms such as pain or paresthesias on quality of life (QOL).

Data from the literature support the assumption that doctors and patients do not always agree on the impact of symptoms on quality of life [35, 36]. Inclusion of the patient's perspective seems mandatory to fully assess the impact of chemotherapy-induced neuropathy.

Quality of life is a uniquely personal perception, denoting the way in which individual patients feel about their health status and/or nonmedical aspects of their lives [37]. Assessment of quality of life is becoming increasingly important as outcome parameter in the evaluation of medical therapies [38–40]. Particularly in palliative care and in oncology practice, quality of life may be just as, or even more important than quantity of life.

The classical outcome parameters such as time to disease progression, survival, and response rates are important, but prolonged life span should preferably be accompanied by satisfactory quality of life as well.

In oncology practice, several general quality of life instruments have been constructed. In the USA the Functional Assessment of Cancer Therapy (FACT-G) questionnaire, and in Europe, the EORTC Quality of Life questionnaire (QLQ-C30), are both used as a core instrument to assess general quality of life aspects in cancer patients [41, 42]. In addition to these general questionnaires, several more disease-specific or therapy-specific submodules/questionnaires have been developed, such as a lung, breast, and brain cancer submodule [43–47].

A chemotherapy-related peripheral neuropathy quality of life questionnaire is lacking in the EORTC approach, although in several EORTC quality of life questionnaires a few questions concerning, e.g., paresthesias, or pain, are incorporated.

Currently, a chemotherapy-induced peripheral neuropathy questionnaire designed for patient self-completion is being constructed in four countries (The Netherlands, UK, France, and Belgium), and three languages (English, French and Dutch) [48]. The guidelines and procedures to be followed during the questionnaire/module development process recommended by the EORTC are being employed [49]. This process consists of four phases: (1) generation of relevant QOL issues; (2) operationalization of the QOL issues into a set of items; (3) pretesting the module questionnaire, and (4) large scale field-testing. The resulting questionnaire/module will be complementary to the EORTC core quality of life questionnaire: the QLQ-C30 [41]. The format of the questionnaire will be the same as the QLQ-C30, which means that patients can indicate to which extent ('not at all', 'a little', 'quite a bit', or 'very much') they have experienced neuropathic complaints during the past week. A potential disadvantage of this method may be that transient symptoms are missed, but this depends on the timing and frequency of the assessments. Besides, a further detailed questionnaire regarding frequency or duration of symptoms would increase the length of the questionnaire, which is a disadvantage in itself.

This project, with an anticipated completion date in 2000, will hopefully yield a patient-based measure of chemotherapy-induced peripheral neuropathy that is both practical and psychometrically sound. In combination with more general quality of life measures, this chemotherapy-induced peripheral neuropathy questionnaire will allow physicians to monitor in a more comprehensive way the impact of peripheral neurotoxic chemotherapy on the daily functional life of patients.

Discussion and recommendations

The kind of evaluation of chemotherapy-induced peripheral neuropathy depends on the endpoint of research. The endpoint may be 'peripheral neuropathy yes/no' due to some kind of chemotherapy regimen, which is completely different from the question whether or not 'dose-limiting peripheral neuropathy' occurs during one chemotherapy regimen compared to another. (Sub)clinical peripheral neuropathy due to chemotherapy can be evaluated with the use of quantitative assessments like nerve conduction velocity studies or quantitative sensory testing. However, test abnormalities usually coincide with clinical symptoms and signs, and will not influence the decision whether or not to retreat a patient with chemotherapy. This decision to retreat is based on the combination of the doctor's perspective (extent of sensory or motor dysfunction) and the patient's perspective, because he/she is the only one who can really judge the burden of chemotherapy-related peripheral neurotoxicity. Therefore, a quality of life assessment should be part of the evaluation.

When multicentre studies are to be undertaken in which neurotoxic chemotherapy regimens and/or potentially neuroprotective agents are used, strict consensus should be sought beforehand with regard to the mode and interpretation of neurotoxicity assessment. We recommend a combination of a standardized scoring system for symptoms and signs, and quality of life

assessment. In our opinion, quantitative assessments (electrophysiological studies or quantitative sensory testing) should only be considered when new neurotoxic chemotherapeutic agents, new neurotoxic chemotherapy combinations, or neuroprotective agents [50] are used. Furthermore, the evaluation of peripheral neurotoxicity should be continued after discontinuation of chemotherapy, in order to study the frequently occurring off-therapy worsening, and, eventually, amelioration of neuropathic symtoms and signs.

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Received 15 November 1999; accepted 2 March 2000.

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