Treatment of Chemotherapy – Induced Peripheral Neuropathy: The Physicians Need Guidelines, the Patients Need Help

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Abstract: The aim of the study was to verify the effectiveness of two methods of introducing standard CIPN-treatment drugs into the therapy.

Materials and Methods: Group A included patients attending weekly appointments, while group B monthly. Standard treatment with amitriptyline, gabapentin (GAB), and oxycodone (OXY) was administered. In group A, the drugs were gradually introduced, while in group B – within one week. After a month and six months of treatment, the therapy effectiveness was assessed by examination of pain intensity (VAS), symptoms of peripheral neuropathy (sNCI-CTC), occurrence of tactile and brush allodynia, and the daily dose of GAB and OXY.

Results: Pain intensity during the study decreased from 5.59 to 2.9 and 2.76 in group A, and from 5.07 to 2.52 and 2.81 in group B. The sNCI-CTC values declined too and were, respectively. 1.9; 1.48; 1.34 in group A and 1.93; 1.52; 1.44 in group B. Tactile allodynia occurred in 15; 5; 5 group A patients and 18; 6; 5 group B patients. Brush allodynia decreased in group A (9; 5; 5) and B (11; 6; 5). The daily GAB dose was 0; 951.72; 927.41 in group A and 900.0; 900.0; 1000.0 in group B. The daily OXY dose was 0; 21.72; 22.07 in group A and 20.0; 20.0; 27.04 in group B; a statistically significant difference was found in the final stage.

The results do not allow recommendation of non-schematic treatment and they should be regarded as a preliminary study. Randomized trials are indispensable for assessment of advantages and drawbacks such treatment.

Keywords: Chemotherapy induced peripheral neuropathy, neuropathy, neuropathic pain, cancer related pain, pain treatment, amitiptyline, gabapentin, oxycodone, treatment schedule, pain, tactile allodynia, brush allodynia.

INTRODUCTION

Standardized treatment of various disease syndromes is generally accepted and desirable practice in all branches of medicine [1]. Since the last decade of the last century, the principles of therapeutic management are based not only on experts' opinions, but also on meta-analyses of randomized trials. This provides a basis for cumulative assessment of available results and formulation of conclusions codified as Evidence Based Medicine [2].

As far as neuropathic pain (NP) is concerned, groups of experts regularly publish guidelines concerning both the effectiveness of particular drugs and their place in therapeutic management of pain syndromes of multiple origins [2-5]. The guidelines are therefore developed in order to enhance the effectiveness and standardization of treatment; still, application of the guidelines sometimes seems to be limited.

The principles of schematic therapeutic management recommend that drugs should be introduced in a specific order until the aim of reducing pain is achieved. Contact with the patient in order to assess the effectiveness of current treatment and recognize the need of introducing subsequent drugs is indispensable. Clinical practice indicates that the patient sometimes has restricted access to the specialist, and general practitioners feel competent to continue the therapy, rather than change it [6, 7]. Strict compliance with the guideline recommendations may significantly prolong the period that is necessary to achieve patient satisfaction. In such cases, the most common procedure is implementation of the recommended treatment scheme disregarding gradual introduction of drugs. Obviously, this involves the necessity of breaching the principles and employing a priori polypragmasia, which the principles normally try to prevent.

The available literature provides only information that this form of therapy is applied by many medical doctors; however, there is no evaluation of its effectiveness [8, 9].

The aim of the study was to compare two models of therapeutic management in patients with chemotherapy-induced peripheral neuropathy (CIPN). In accordance with the NP management guidelines, the first group of patients received drugs sequentially, and the patients in the second group were given all drugs simultaneously.

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Table 1: Criteria of Inclusion and Exclusion from the Study

Inclusion criteria	Exclusion criteria
Chemotherapy received during the last year	Metastases to the central nervous system
The last chemotherapy cycle received 3 weeks earlier	Paraneoplastic syndrome
No planned oncological therapy (chemotherapy, radiotherapy, surgery) during the next 3 months	Pathological fractures and vertebral metastases, if combined with neurogenic or neuropathic pain
CIPN symptoms persisting for longer than 3 weeks	Previous peripheral neuropathies
No current treatment	Other locations of pain if the patient cannot discriminate it
VAS ≥ 5/10	
sNCI-CTC ≥ 1/4	
Consent to participate in the study	

VAS – Visual Analogue Scale; sNCI-CTC - sensory National Cancer Institute – Common Toxicity Criteria.

MATERIAL AND METHOD

The study involved patients of the pain management outpatient clinic at the Institute of Rural Health in Lublin who received treatment for CIPN between August 2011 and February 2012.Criteria for exclusion from and inclusion into the study are presented in Table **1**.

Fifty nine patients were qualified for the study and divided into two groups depending on their ability to contact the pain management outpatient clinic. The type of cancer disease and chemotherapy applied are presented in Table **2**. Group A was composed of patients who were capable of attending weekly appointments, whereas those who had transport-related problems were classified as group B.

Table 2: Types of Cancer Disease and Therapy in Both Patient Groups

		Group A n =	Group B n =
Type of cancer	Breast cancer	8	8
	Ovarian cancer	7	2
	Uterine cancer	0	2
	Lung cancer	4	5
	Colorectal cancer	6	7
	Prostate cancer	4	3
Therapy	Platinum derivatives	12	17
	Taxans	8	7
	Vinca alkaloids	9	3

After taking patient's history and analysing the medical record, each patient underwent general medical examination and short neurological examination. During qualification for the study, only those patients who met all inclusion criteria, did not fulfil any of the exclusion criteria, and gave informed consent to participate in the study were accepted. Pain intensity ≤ 3 measured with the Visual Analogue Scale (VAS), symptoms of neuropathy ≤ 2 in the sensory National Cancer Institute – Common Toxicity Criteria (sNCI-CTC) scale, and absence of tactile and brush allodynia were regarded as a therapeutic success. Figure **1** presents schemes of introduction of drugs in both groups.

When the previous treatment failed, patients from group A received drugs sequentially during the weekly visits. On the fourth visit, gabapentin or oxycodone doses were adjusted according to pain intensity. In the case of patients who had no possibility of regular contact with the pain management outpatient clinic (Group B), drugs were introduced in accordance with an appropriate scheme during the first visit (Figure **1**). After four weeks of treatment, all the parameters observed were re-evaluated and the daily gabapentin and oxycodone doses were adjusted. The therapy was continued and the drug doses were adjusted monthly according to the severity of symptoms. The observations of all the patients were discontinued after six months and all the parameters were evaluated. Throughout the study period, patients in both groups were in telephone contact with the doctor. In the cases of persisting side effects, discontinuation of medication was only recommended by telephone, and the therapy was not adjusted until the patient visited the pain management clinic.

The results obtained were statistically analyzed. The differences in the non-parametric (tactile/brush allodynia) were estimated using the χ^2 test, whereas the differences in pain intensity in the VAS scale, severity of peripheral neuropathy symptoms in the sNCI-CTC scale, and daily gabapentin and oxycodone doses were assessed with the t-Student test for related

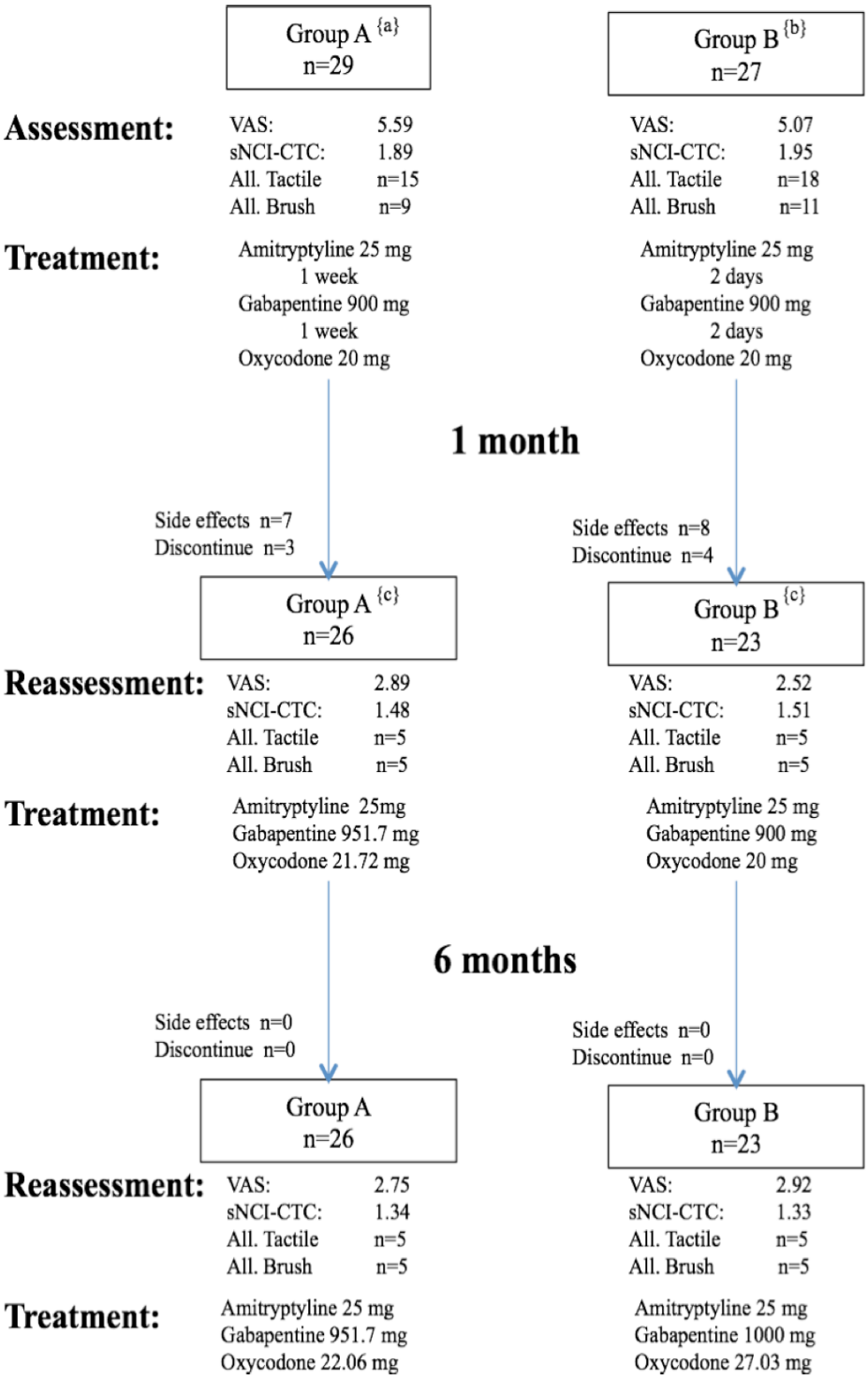

Figure 1: Treatment schemes applied in both patient groups.
Abbreviations: VAS-Visual Analogue Scale; sNCI-CTC- sNCI-CTC - sensory National Cancer Institute – Common Toxicity Criteria; All. – Allodynia.
{a} – initial visit, weekly subsequent visits and telephone contact.
{b} - initial visit and telephone contact.
{c} – monthly reassessment.

and unrelated groups. $p < 0.05$ was deemed statistically significant. The statistical analysis was performed with the statistical package Statgrafix 5 Plus. The study was approved by the Bioethical Committee of the Institute of Rural Health in Lublin.

RESULTS

The study was conducted initially on 56 patients (Group A n = 29, Group B n = 27), 49 of whom remained throughout. Females constituted 50% (n=28) of all the patients. The reasons for exclusion were persistent adverse side effects. Discontinuation of the treatment was recommended for similar numbers of patients in both groups (Group A n=3; Group B n=4) and took place during the first month of the therapy. The results of the observations are presented in Table **3**.

After the first month of the treatment, comparable reduction in both pain intensity and severity of neuropathy syndromes, as well as in tactile and brush allodynia was achieved. The parameters did not change until the end of the observation period. Both

Table 3: Presentation of all Parameters Assessed During the Subsequent Stages of the Study

	Initial	After 1 month	After 6 months
Scores and symptoms			
VAS	score/10		
Group A	5.59 (1.13)	2.9 * (0.80)	2.76 * (0.86)
Group B	5.07 (0.90)	2.52 * (0.79)	2.81 * (0.72)
sNCI-CTC	score/4		
Group A	1.90 (0.77)	1.48 * (0.51)	1.34 * (0.48)
Group B	1.93 (0.73)	1.52 * (0.51)	1.44 * (0.51)
Tactile allodynia	n=		
Group A	15 51.72%	5 [a] 19.23%	5 [a] 19.23%
Group B	18 66.67%	6 [a] 26.09%	5 [a] 21.74%
Brush allodynia	n=		
Group A	9 31.03%	5 [a] 19.23%	5 [a] 19.23%
Group B	11 40.74%	6 [a] 26.09%	5 [a] 21.74%
Medication			
Oxycodone	mg/day		
Group A	–	21.72 (5.3)	22.07 * (6.09)
Group B	20.00 (0.00)	20.00 (0.00)	27.04 *, ‡ (9.12)
Gabapentin	mg/day		
Group A	–	951.72 (138.02)	927.41 * (169.98)
Group B	900.00 (0.00)	900.00 (0.00)	1000.00 * (182.57)

The parametric values are presented as mean values (standard deviation below). The numbers of patients in the groups are presented as absolute values and per cent of the group studied.
Daily doses of the drugs are presented in milligrams as mean values (standard deviation below).
*- a statistically significant difference in comparison to the baseline values or values after 1 month of the observations determined with the t-Student test.
[a] - a statistically significant difference in comparison to the baseline values determined with the χ^2 test.
‡- a statistically significant difference between the groups determined with the t-Student test.

modes of treatment resulted in reduced tactile and brush allodynia within the first month of the therapy, likewise in the case of the other parameters mentioned above.

After a month's therapy, the mean daily dose of gradually introduced gabapentin was slightly higher in group A than the dose arbitrarily established for group B, but the difference was not statistically significant. During the six months of further treatment, patients from group B required continually increasing doses of the drug so that the therapeutic effect could be maintained. In group A, there was no such necessity; moreover, the final results demonstrated a slight reduction in the daily dose.

Similar trends were observed in the case of the oxycodone therapy. After the six-month therapy, it was demonstrated than group B required a significantly higher daily dose than group A for adequate pain control.

DISCUSSION

Treatment standards are regarded by most practitioners as valuable guidelines for achievement of "therapeutic success". However, therapeutic management that does not fully comply with the standard requirements frequently produces the desired therapeutic effects. Therefore, a question arises whether the standards should be regarded as the only method of achieving the purpose.

One of the best-known standards of pain management commonly used worldwide is the WHO analgesic ladder. The basic principle of this algorithm assumes progression to the consecutive grades of the analgesic ladder when the drugs used are not effective.

This sometimes requires patience from both the patient and the doctor; therefore, in spite of long-term experience, this principle has been repeatedly verified [10-13]. The main idea behind using strong opioids directly after administration of non-steroid anti-inflammatory drugs (NSAID) was not to refute the proven algorithm, but to provide the patient with adequate pain control [10]. Such management has appeared effective in many cases and clinical practice has demonstrated that small doses of "strong opioids" can successfully replace second-grade drugs from the WHO analgesic ladder [11-13].

A similar problem arises during NP therapy, in particular treatment of CIPN. The pathophysiology of this pain syndrome is highly diverse and largely depends on the type of cytostatic drugs applied in causal treatment [14, 15]. In other diseases, e.g. postherpetic neuralgia or diabetic polyneuropathy, the pathomechanism of damage to the peripheral nervous system (PNS) has been elucidated and adequate management algorithms have been developed. CIPN is a form of NP, which still raises doubts as to the modes of diagnosis and treatment standards [16, 17]. Therefore, the adopted principle of treatment is still based on analogies between this disease and other NP types.

It is only recently that the algorithm of treatment of cancer-related NP applied in CIPN-affected patient has been evaluated [18]. The conclusions of the study confirm the effectiveness of the 12-week therapy programme. The study carried out by Richardson *et al*. [19] showed that regular neurological examination allows modification of therapy which reduces the incidence of CIPN. There is still an unresolved problem whether the time within which patient's improvement is achieved can be shortened.

The attempt to employ complex treatment without a temporal regime was aimed at achieving more rapid reduction in pain intensity. The comparison of the two modes of introduction of the same drugs (amitriptyline, gabapentin, oxycodon) into the treatment demonstrated similar efficacy of both methods; therefore, the possibility of concurrent, rather than gradual application of all the aforementioned drugs cannot be excluded.

A major limitation of this study was the small group of patients and lack of randomization.

Although comparable improvement of systematically treated patients and those who were unable to report to the clinic regularly was achieved, the patients treated without a scheme required higher doses of both gabapentin and oxycodone within the six months. Therefore, it cannot be excluded that gradual introduction of drugs may modify the complex mechanisms regulating perception of NP and sensitivity to the treatment. This has a psychological aspect as wall, as the patient is given a sense of participating in the treatment and co-responsibility for it.

It was important from the point of view of medical practice that the severity of side effects and hence the numbers of patients forced to discontinue the therapy were comparable in both groups. Therefore, it can be assumed that the therapy diverging from the scheme

did not pose a threat to the patients. The data presented in the paper do not allow recommendation of the proposed non-schematic methods of treatment and they should be regarded as a preliminary study. Randomized trials are indispensable for detailed assessment of possible advantages and shortcomings of such management. The issue whether the period of waiting for the analgesic effect of drugs can be shortened is still to be discussed.

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