Chemotherapy-Induced Peripheral Neuropathy (CIPN) in Patients Receiving 4-6 Cycles of Platinum-Based and Taxane-Based Chemotherapy: A Prospective, Single-Center Study from Kosovo

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is most commonly associated with platinum-based drugs, taxanes, and vinca alkaloids. This prospective study from a single center in Kosovo aimed to evaluate CIPN in 120 patients receiving 4-6 cycles of platinum-based and taxane-based chemotherapy.

Material/Methods: One hundred twenty patients underwent neurological examination and nerve conduction studies (NCS) before chemotherapy, and after 4 to 6 cycles of treatment. Sixty patients were treated with platinum-based chemotherapy, 30 were treated with taxane-based chemotherapy, and 22 patients received a combination of platinum- and taxane-based chemotherapy. The most commonly used platinum-based compounds were oxaliplatin and carboplatin, whereas the most commonly used taxane medications were paclitaxel and docetaxel. Presence of neuropathy was confirmed with neurological examination of electrophysiological criteria applicable for polyneuropathies. Total Neuropathy Score (TNSr) was used to combine clinical and electrophysiological values.

Results: Around 90% of patients self-reported neuropathic symptoms, and in 60% of them polyneuropathy was present in NCS. All sensory and motor nerves had significantly lower amplitudes (P<0.01). Platinum-based agents caused more pronounced decrease in ulnar nerve compound motor action potential (CMAP) (P<0.05); when used solely or in combination with taxanes, they caused significant decrease in tibial nerve CMAP (P<0.01). TNSr did not reach statistical significance between groups; only clinical muscle strength showed pronounced weakness in the combined protocol (P<0.05).

Conclusions: These findings support previous studies and show that CIPN, including sensory and motor symptoms, is commonly associated with chemotherapy. Platinum-based chemotherapy agents were more commonly associated with ulnar and tibial nerve damage in this study population.

Keywords: Ulnar Nerve • Tibial Nerve • Polyneuropathies • Chemotherapy, Adjuvant

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Background

Chemotherapeutic or cytostatic drugs are chemical agents used for treating solid cancers and hematological neoplastic diseases. While the aim is to fight rapidly differentiating malignant cells, chemotherapy drugs are not selective toward the targets. These medications also damage normal cells and tissues, especially those which differentiate quickly, like those in the gastrointestinal, skin, and hematopoietic systems [1].

Among the many kinds of damage that chemotherapy can cause, of utmost importance for nerve physiology is peripheral nervous system damage, leading to chemotherapy-induced peripheral neuropathy (CIPN). The terminal parts of axons and support cells in the peripheral nervous system are sensitive to these drugs. Damage to those structures is caused through a range of pathophysiological mechanisms [2].

Epidemiological registers show that CIPN is present in 30-55% of patients treated with chemotherapy [3,4]. This figure covers a wide range of conditions because not all chemotherapy drugs cause CIPN: some of them are known to cause severe damage, while others are not known to cause any harm. In most of the patients with polyneuropathy, the severity can last and progress even months after chemotherapy ends, a phenomenon described as the “coasting effect” [5]. The drugs most linked to CIPN are platinum-based compounds (eg, cisplatin, carboplatin, oxaliplatin) [6], antimitotic agents like taxanes (eg, paclitaxel, docetaxel) [7-9], vinca alkaloids (eg, vincristine, vinblastine, vinorelbine, vinflunine) [10], protease inhibitors (eg, bortezomib) [11], thalidomide [12], alkylating agents (eg, cyclophosphamide, procarbazine) [13], and antimetabolites (eg, methotrexate, cytosine arabinoside, gemcitabine, 5-fluorouracil, capecitabine).

The severity of CIPN correlates with the cumulative dose of administered medication. In the absence of clear therapeutic options, limiting the treatment time and dose to the minimal effective level is presently the most beneficial method for prophylaxis of this complication [14]. The recently updated American Society of Clinical Oncology (ASCO) guidelines have not found additional studies supporting the use of any preventative approach for neuropathy [15]. Beside the medication type and its cumulative dose, other factors that stem from medication and affect the manifestation of polyneuropathy are infusion speed and frequency, administration method, and treatment protocol. Patient factors relevant to CIPN include pre-existing polyneuropathy, concomitant diseases, and surgery [16].

The diagnosis of CIPN can be established by clinical history and by development of symptoms and signs attributable to neuropathy. Neurologic electrodiagnostic tests such as nerve conduction studies (NCS) and electromyography (EMG) are used to evaluate the peripheral nervous system, but in the case of CIPN they often lack the capacity to detect changes in otherwise clinically present neuropathy [15,17]. This derives from the limitation of NCS being able to detect changes only in thick and myelinated fibers [17]. Overall, CIPN is clinically characterized by the appearance of tactile symptoms, initially in distal parts of the extremities, progressing to more proximal parts. Motor symptoms often follow the sensory ones, are less pronounced, and rarely cause functional difficulties [18]. Distal axonopathy is the most frequent form of CIPN. It reflects damage to axonal function and transport that leads to retrograde Wallerian type of degeneration of the terminal parts of sensory axons [19].

There are some general toxicity scales in use, such as the WHO scale, the National Cancer Institute Common Toxicity Criteria 3.0, and the Eastern Cooperative Oncology Group (ECOG) scale [20]. There are also some more specific scales in the field of neurology that are more suitable for assessing the clinical and electrophysiological features of peripheral nerve involvement due to chemotherapy treatment. Of these, the Total Neuropathy Score (TNS) is easy to use and provides more specific neuropathy information [21]. A reduced version was used in the present study.

This prospective study from a single center in Kosovo aimed to evaluate CIPN in 120 patients receiving 4-6 cycles of platinum-based and taxane-based chemotherapy.

Material and Methods

The Ethics Commission of the University of Prishtina “Hasan Prishtina” approved the present study. Patient information consent forms informed patients with the name, goals, methods to be used, possible adverse events, and of the expected benefit of the study. It stated that the participation is voluntary and the information gathered would be confidential, shared only with the authors, and used solely for the purposes of this study. Consent was signed by all participating patients for all clinical and electrophysiological examinations.

Cases

Clinical and electrophysiological evaluations prior initiation of chemotherapy, and after 4-6 cycles of chemotherapy treatment, were done in 120 subjects (63 females and 57 males). All of the patients had been diagnosed with cancer. The cancer type was irrelevant for this study. All pre-chemotherapy measurements had to be within normal physiologic ranges; patients with previously diagnosed polyneuropathy or other conditions known to cause polyneuropathy were excluded from the study.
Clinical Evaluation

All patients were asked to self-report sensory, motor, and autonomic symptoms. They were recorded within the TNSr grading. Patients underwent identical neurological examination before and after the chemotherapy treatment, with emphasis on clinical evaluation of muscle strength, superficial sensitivity, deep sensitivity, deep-tendon reflexes, and autonomic symptoms.

Muscle strength evaluation consisted of grading the force of the respective key muscles in the upper and lower extremities through evaluation of their full range of movement. Patients were first asked to perform physiological movements of a muscle to its optimal position and hold it against gravity for 5 sec. Later, the examiner applied optimal counterforce against the muscle and evaluated the resistance. Muscles evaluated were deltoid, biceps, triceps, hand extensor and flexor, hand finger flexor and abductor muscles, iliopsoas, quadriceps femoris, anterior tibial, and gastrocnemius muscles. The muscle strength was graded by using the Oxford scale (0 for no movement up to 5 for full range of movement, resistant against examiner counterforce) [22].

In regard to superficial sensitivity, patients were examined for sensitivity to touch, pain, and two-point discrimination modalities. Decrease of touch and pain sensation and/or inability to discriminate qualitative stimulation between 2 points were considered to be pathologic [23]. Deep sensitivity was evaluated using a standardized tuning vibration fork (128 Hz). Examiner activated it by hitting the palm, and the stem was placed in the distal interphalangeal joint of the index finger and great toe. Time passed from the activation of the tuning fork and its placement until the cessation of vibration feeling by the patient was recorded and compared to the examiner’s perception. Earlier cessation of feeling by the patient was considered pathologic [24].

Deep-tendon reflexes (DTR) were measured based on conventional grading from 0, which indicates no response, to 4, which indicates a repeating reflex, usually called clonus [25].

Electrophysiological Methods

All patients underwent an identical protocol of electrophysiological study, which consisted of nerve conduction studies for certain sensory and motor nerves in the right upper and lower extremities. For the purposes of NCS, the MEB-9400K Neuropack S1 EMG/EP Measuring System of Nihon Kohden was used. The temperature of the patients’ extremities was 35°C. Their extremities were heated if necessary.

Surface electrodes were used for NCSs. The stimulating electrode was placed above the respective nerve (for sensory nerves) or muscle (for motor nerves). Right median, ulnar, and sural nerves were examined for sensory nerve conduction studies. Median and ulnar responses were recorded orthodromically, whereas sural response was recorded antidromically. Parameters recorded were distal latency, amplitude of the sensory nerve action potential (SNAP), and the nerve conduction velocity.

For motor nerve conduction evaluation, right median, ulnar, peroneal, and tibial nerves were selected. The peak latency, the amplitude of compound muscle action potential (CMAP), and the nerve conduction velocity were determined. Decreased sensory nerve action potential (SNAP) and/or compound motor action potential (CMAP) amplitudes and decreased nerve conduction velocities were considered to be diagnostic for presence of neuropathy.

The clinical and electrophysiological observations were combined and scaled into the Total Neuropathy Score (TNS). This scale occurs in 2 variants: the reduced score (TNSr), which combines the electrophysiological and clinical observations, and a clinical score (TNSc), which uses clinical observations only [21]. We used the reduced Total Neuropathy Score because of its documented correlation with polyneuropathic changes [5,21]. The reduced version of the TNS consists of information on 9 parameters: sensory symptoms, motor symptoms, autonomic symptoms, pin sensitivity, vibration sensitivity, strength, DTR, sural nerve SNAP, and peroneal nerve CMAP. Based on the findings, each category is graded as 1 to 4 points, with the total score ranging from 0 (absence of any sign of neuropathy) to 36 (full neuropathy).

Statistical Analysis

Descriptive statistics – mean, standard deviation, minimum, and maximum – were calculated for each of the examined parameters. The means were compared parametrically (t test and ANOVA) using SPSS v. 26. The threshold for statistical significance was 0.05.

Results

Patients were selected from the Oncology Clinic of the University Clinical Center of Kosovo (UCCK), and their clinical and electrophysiological evaluation was performed in the Neurology Clinic of UCCK. Examined patients were almost equally divided by sex (63 females to 57 males), and their mean age was 59.4 ± 11 years. They had been diagnosed with various cancers and were expecting to begin chemotherapy treatment (Table 1). Breast, gastric, colon, and lung cancers were the most frequent diagnoses.
Patients were treated with 15 different chemotherapy protocols (Table 2). Approximately 93% (112 of 120) of them had either platinum-based compounds or taxanes, or both of them, at the core of the regimen. Oxaliplatin and carboplatin were the most frequently used platinum-based agents, whereas the most often used taxane medications were paclitaxel and docetaxel. Platinum-based and/or taxane agents were usually combined with alkylating agents (eg, cyclophosphamide), antimetabolites (eg, capecitabine, 5-fluorouracil) and doxorubicin, in different combinations.

Since almost all protocols included platinum-based and/or taxane agents, and because these are mostly associated with CIPN, we continued with the comparison of clinical and electrophysiological findings between patients treated with platinum-based medications only, taxanes only, or both (Table 3).

Almost 90% of patients self-reported sensory symptoms. In almost two-thirds of them, these symptoms were localized in the fingers, hands, and feet, predominantly in the lower extremities. A few patients reported minor motor and/or autonomous dysfunction. Objective physical sensory tactile dysfunction was shown in 75% of patients, with changes reported mostly in the hands and feet, and rarely extending to more proximal parts. Diminished vibration sensitivity was detected at a similar frequency and distribution with tactile dysfunction. Muscle strength was generally well preserved.

In initial (pre-chemotherapy) assessment, sensory and motor responses were within normal limits in 120 examined patients. After 4-6 chemotherapy cycle treatments, the sensory sural responses were not obtained in 64 patients, the ulnar responses were not obtained in 19, while sural responses were not obtained in 23. The SNAPs of all sensory nerves were significantly lower (P<0.001). The conduction velocities of the

Table 1. Type of diagnosed cancer and distribution by number, age, and sex.

| Cancer type | Number | Age (Mean±SD) | Female/Male |
|-------------|--------|---------------|-------------|
| Breast      | 24     | 55.4±12.8     | 24/0        |
| Oro-esophageal | 3     | 57.6±14.4     | 2/1         |
| Gastric     | 18     | 60±8.2        | 4/14        |
| Colon       | 22     | 62.7±8.1      | 10/12       |
| Rectal      | 4      | 69±5.4        | 2/2         |
| Lung        | 17     | 63±7.4        | 2/15        |
| Pancreatic  | 8      | 58.3±8.7      | 5/3         |
| Ovarian     | 7      | 57±14.3       | 7/0         |
| Endometrial | 3      | 60.3±8.6      | 3/0         |
| Testicular  | 1      | 34            | 0/1         |
| Germ cell   | 2      | 37±19.7       | 2/1         |
| Gallbladder | 3      | 59.3±5.1      | 1/2         |
| Urinary     | 2      | 70±7.0        | 0/2         |
| Renal cell  | 1      | 55            | 1/0         |
| Pharyngeal  | 1      | 66            | 0/1         |
| Laryngeal   | 2      | 61±1.4        | 0/2         |
| Melanoma    | 1      | 55            | 0/1         |
| Hodgkin     | 1      | 26            | 1/0         |
| Subtotal    | Female: 63 | Female: 57.9±11.7 | |
| Total       | Male: 57 | Male: 60.9±10.1 | |
|             | 120     | 59.36±11.0    | 63/57       |

SD – standard deviation.

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The CMAPs and velocities of the median, tibial, peroneal (all $P<0.001$), and ulnar ($P<0.01$) nerves were significantly lower and slower, respectively ($Table 5$).

Treatment with platinum-based compounds had a more pronounced effect in decreasing ulnar nerve CMAP ($P<0.05$), while protocols using platinum compounds only or in combination with taxanes led to significant decrease in tibial nerve CMAP ($P<0.01$) ($Table 6$).

Table 2. Chemotherapy protocols.

| Treatment regimen       | Number | Age (Mean±SD) |
|-------------------------|--------|---------------|
| Platinum only           | 2      | 61±1.4        |
| Platinum + Taxane       | 20     | 62.5±10.7     |
| Platinum + Antimetabolites | 53    | 61.45±8.4    |
| Platinum + Taxane + Doxorubicin | 1  | 55          |
| Platinum + Taxane + Antimetabolites | 1 | 58          |
| Platinum + Doxorubicin + Antimetabolites | 1 | 50          |
| Platinum + Dacarbazine  | 1      | 55            |
| Platinum + Etoposide    | 4      | 44.5±19.3     |
| Taxane + Antimetabolites | 6     | 58.6±8.0      |
| Taxane + Doxorubicin    | 2      | 70±7.0        |
| Taxane + Doxorubicin + Alkylating | 20  | 55±13.1      |
| Irinotecan + Antimetabolites | 3  | 65.6±4.6     |
| Alkylating + Doxorubicin| 4      | 57.7±13.4     |
| Doxorubicin + Vinblastin + Dacarbazine + Bleomycin | 1  | 26           |
| Taxane + Antimetabolites + Etoposide | 1 | 51           |
| **Total**               | **120**| **59.36±11.0**|

SD – standard deviation.

Table 3. Chemotherapy protocols based on platinum- and taxane-based compounds.

| Treatment regimen based on Platinum and/or Taxane | Number | Age (Mean±SD) |
|--------------------------------------------------|--------|---------------|
| Neither platinum nor taxane                      | 8      | 56.7±15.8     |
| Platinum only and/or combination                 | 60     | 60±10.1       |
| Taxane only and/or combination                    | 30     | 56.7±11.8     |
| Platinum + Taxane and/or combination              | 22     | 62±10.3       |
| **Total**                                         | **120**| **59.36±11.0**|

SD – standard deviation.

sensory median ($P<0.001$), and ulnar ($P<0.05$) nerves were significantly slower ($Table 4$).

The CMAPs and velocities of the median, tibial, peroneal (all $P<0.001$), and ulnar ($P<0.01$) nerves were significantly lower and slower, respectively ($Table 5$).

Treatment with platinum-based compounds had a more pronounced effect in decreasing ulnar nerve CMAP ($P<0.05$), while protocols using platinum compounds only or in combination with taxanes led to significant decrease in tibial nerve CMAP ($P<0.01$) ($Table 6$).

The mean TNSr after chemotherapy was 11.2 (8.5 for no platinum/taxanes regimen, 12.1 for platinum-based, 9.6 for taxane-based, and 11.6 for platinum+taxanes). TNSr did not show any significant difference among groups. Only muscle strength was significantly decreased in patients treated with the combination of platinum- and taxane-based compounds ($P<0.05$) ($Table 7$).

**Discussion**

Chemotherapy drugs damage peripheral nerve fibers to varying degrees, thus leading to polyneuropathy. Almost all patients...
were treated with platinum- and/or taxane-based compounds. These agents are mostly linked to peripheral nerve damage and thus a high degree of self-reported sensory symptoms, and objective clinical findings supported neuropathy in our cohort. Terminal parts of axons and the supportive cells of the peripheral nervous system are prone to damage by these drugs through various pathophysiological mechanisms [2]. Two-thirds of the cohort reported moderate to severe sensory symptoms in distal parts of the extremities, associated with diminished deep-tendon reflexes and vibration sensitivity. If mild symptoms are included, then almost 90% of patients described sensory symptoms. In most of these cases, symptoms were reported to have manifested after the third or fourth treatment cycle. Even though almost 90% of patients self-reported sensory symptoms, an objective decrease in sensitivity was found in 75% of them. Other major studies have reported similar sensory system involvement due to chemotherapy exposure [3,26-29]. Muscle strength was generally preserved, with a very few cases of mild decrease in strength, which were more

| Nerve            | Parameter       | Pre-treatment value (Mean±SD) | Post-treatment value (Mean±SD) | Significance |
|------------------|-----------------|-------------------------------|-------------------------------|--------------|
| Median nerve (N: 97) | Distal latency (ms) | 2.2±0.3                      | 2.6±0.4                      | p<0.001      |
|                  | Velocity (m/s)  | 54.6±6.8                      | 49.7±8.7                      | p<0.001      |
|                  | Amplitude (µV)  | 23.7±10.7                     | 12.9±10.1                     | p<0.001      |
| Ulnar nerve (N: 101) | Distal latency (ms) | 1.9±0.3                      | 2.4±1.5                      | p<0.01       |
|                  | Velocity (m/s)  | 54.0±6.9                      | 49.9±10.0                     | p<0.05       |
|                  | Amplitude (µV)  | 13.9±5.4                      | 8.9±8.3                       | p<0.001      |
| Sural nerve (N: 56)  | Distal latency (ms) | 2.3±0.3                      | 2.4±0.3                      | p=0.246      |
|                  | Velocity (m/s)  | 53.6±7.4                      | 51.3±8.3                      | p<0.05       |
|                  | Amplitude (µV)  | 16.5±5.5                      | 8.2±6.0                       | p<0.001      |

SD – standard deviation.

| Nerve            | Parameter       | Pre-treatment value (Mean±SD) | Post-treatment value (Mean±SD) | Significance |
|------------------|-----------------|-------------------------------|-------------------------------|--------------|
| Median nerve (N: 119) | Distal latency (ms) | 3.2±0.6                      | 3.7±0.8                      | p<0.001      |
|                  | Velocity (m/s)  | 59±6.3                        | 52±7.2                        | p<0.001      |
|                  | Amplitude (mV)  | 8.9±2.4                       | 6.6±2.4                       | p<0.001      |
| Ulnar nerve (N: 119) | Distal latency (ms) | 2.6±0.4                      | 2.8±0.5                      | p<0.01       |
|                  | Velocity (m/s)  | 61.3±7.0                      | 58.2±8.9                      | p<0.01       |
|                  | Amplitude (mV)  | 7.6±1.6                       | 6.9±2.2                       | p<0.01       |
| Tibial nerve (N: 105) | Distal latency (ms) | 4.5±1.2                      | 5.3±1.3                      | p<0.001      |
|                  | Velocity (m/s)  | 46.0±5.5                      | 41.6±5.1                      | p<0.001      |
|                  | Amplitude (mV)  | 8.1±3.3                       | 5.1±3.4                       | p<0.001      |
| Peroneal nerve (N: 103) | Distal latency (ms) | 4.3±1.1                      | 4.5±1.3                      | p=0.515      |
|                  | Velocity (m/s)  | 49.9±6.7                      | 44.1±8.4                      | p<0.001      |
|                  | Amplitude (mV)  | 4.6±1.8                       | 2.7±1.8                       | p<0.001      |

SD – standard deviation.
Table 6. Electrophysiological values comparison between platinum-only, taxane-only, and combination groups.

| Variable                          | None (Mean±SD) | Platinum (Mean±SD) | Taxane (Mean±SD) | Combination (Mean±SD) | Significance |
|----------------------------------|----------------|-------------------|-----------------|-----------------------|--------------|
| Sensory median amplitude (μV)    | 18.0±7.5 (N: 6) | 10.6±7.6 (N: 46)  | 16.3±14.3 (N: 25)| 12.2±8.3 (N: 20)     | p=0.08       |
| Sensory median velocity (m/s)    | 58.4±10.3 (N: 6)| 48.3±8.3 (N: 46)  | 49.5±9.4 (N: 25) | 50.3±7.1 (N: 20)     | p=0.06       |
| Sensory ulnar amplitude (μV)     | 9.7±3.7 (N: 7)  | 6.9±5.1 (N: 51)   | 12.1±12.5 (N: 24)| 9.8±8.5 (N: 19)      | p=0.07       |
| Sensory ulnar velocity (m/s)     | 56.1±7.2 (N: 7) | 48.4±9.6 (N: 51)  | 52.9±11.6 (N: 24)| 47.9±8.7 (N: 19)     | p=0.07       |
| Sensory sural amplitude (μV)     | 11.3±7.0 (N: 6) | 6.9±5.2 (N: 26)   | 9.0±5.5 (N: 15)  | 8.8±8.0 (N: 9)       | p=0.36       |
| Sensory sural velocity (m/s)     | 53.1±6.0 (N: 6) | 49.1±7.8 (N: 26)  | 52.0±9.3 (N: 15) | 55.2±8.4 (N: 9)      | p=0.23       |
| Motor median amplitude (mV)      | 6.9±2.2 (N: 8)  | 6.3±2.2 (N: 59)   | 7.0±2.9 (N: 30)  | 7.0±2.5 (N: 22)      | p=0.43       |
| Motor median velocity (m/s)      | 50.9±4.0 (N: 8) | 52.2±6.9 (N: 59)  | 52.8±9.8 (N: 30) | 52.7±4.9 (N: 22)     | p=0.94       |
| Motor ulnar amplitude (mV)       | 8.4±3.2 (N: 8)  | 6.4±1.9 (N: 59)   | 7.4±2.4 (N: 30)  | 6.9±2.2 (N: 22)      | p<0.05       |
| Motor ulnar velocity (m/s)       | 58.4±7.4 (N: 8) | 58.3±9.0 (N: 59)  | 58.7±11.5 (N: 30)| 56.9±4.3 (N: 22)     | p=0.90       |
| Motor tibial amplitude (mV)      | 9.0±5.4 (N: 7)  | 4.6±2.5 (N: 51)   | 5.6±4.1 (N: 27)  | 4.5±2.5 (N: 20)      | p<0.05       |
| Motor tibial velocity (m/s)      | 44.0±4.4 (N: 7) | 41.5±5.4 (N: 51)  | 41.4±5.6 (N: 27) | 41.1±4.1 (N: 20)     | p=0.63       |
| Motor peroneal amplitude (mV)    | 2.4±1.3 (N: 7)  | 2.7±1.8 (N: 50)   | 2.9±2.1 (N: 27)  | 2.5±1.3 (N: 19)      | p=0.88       |
| Motor peroneal velocity (m/s)    | 47.5±4.7 (N: 7) | 44.1±7.6 (N: 50)  | 45.3±8.4 (N: 27) | 41.4±10.8 (N: 19)    | p=0.29       |

SD – standard deviation.

Table 7. Clinical comparison between platinum-only, taxane-only, and combination groups.

| Variable                         | None     | Platinum | Taxane   | Combination | Significance |
|----------------------------------|----------|----------|----------|-------------|--------------|
| Sensory symptoms                 | 1.50     | 1.95     | 1.47     | 1.73        | p=0.17       |
| Motor symptoms                   | 0.00     | 0.15     | 0.07     | 0.23        | p=0.30       |
| Autonomous symptoms              | 0.00     | 0.05     | 0.00     | 0.00        | p=0.38       |
| Tactile sensitivity              | 1.25     | 1.40     | 1.20     | 1.36        | p=0.84       |
| Vibration sensitivity            | 0.75     | 1.23     | 0.80     | 1.05        | p=0.10       |
| Muscle strength                  | 0.00     | 0.18     | 0.07     | 0.55        | p=0.05       |
| Deep-tendon reflexes             | 2.00     | 2.77     | 2.30     | 2.55        | p=0.21       |
| Total Neuropathy Score, reduced  | 8.5±5.1  | 12.1±5.8 | 9.6±5.5  | 11.6±6.5    | p=0.14       |
pronounced in the groups treated with platinum compounds only or in combination with taxanes [30].

We were unable to obtain sensory sural response from 64 patients, ulnar response from 19, and median response from 23. The SNAPs for all sensory nerves were lower in patients after chemotherapy. These findings indicated axonal degeneration in the sensory fibers of these nerves, and corroborated previously reported cases of platinum and taxane exposure [9,14,30]. There was no significant difference in sensory nerve involvement between exposures to different types of chemotherapy drugs.

The CMAPs and velocities of the tibial, median, peroneal, and ulnar nerves were lower and slower, respectively. Slowing seems to be a consequence of axonal degeneration rather than primary demyelinating neuropathy. Despite decreased CMAPs, the absence of significant prolongation in distal latencies also suggested primarily axonal involvement of the peripheral nerves, corroborating the predominantly axonal involvement reported in previous studies [30-33]. Treatment with platinum-based compounds resulted in a greater decrease in motor ulnar and tibial nerve CMAPs in comparison to taxane-based chemotherapy regimens; this finding has not been reported by other studies involving treatment with both options in their cohort [26,28,30].

Reported symptoms and detected signs were mainly sensory which, in the case of platinum compounds, is suggested to derive from the accumulation of the toxin in dorsal root ganglia (DRG) and by initiating axonal hyperexcitability and repetitive discharges via changes in the voltage-gated sodium channels [29,34-37]. These agents are believed to have a strong affinity for the DNA of these neurons [38] which, while important for antineoplastic purposes, is apoptotic for the neurons [14]. Most motor neurons have larger diameters and are highly myelinated; motor nerve involvement is usually present when sensory involvement is more pronounced [19].

Susceptibility to damage is associated with length, diameter, and myelination of nerve fibers. Since no significant difference was found in length and myelination between median and ulnar nerves, and tibial and peroneal nerves, respectively, these 2 factors do not appear to explain the more pronounced ulnar and tibial nerve involvement in patients treated with platinum-based compounds. Based on ultrasonographic measurements of the cross-sectional areas and maximal thicknesses of peripheral nerves, ulnar and tibial nerves have larger mean cross-sectional area than median and peroneal nerves, respectively [39-41]. A larger cross-sectional area is associated with increased susceptibility to nerve damage, as shown in previous studies. However, this finding cannot fully explain our observations, since those investigations were conducted for peripheral nerve entrapment cases, where the underlying polyneuropathy mechanism is different. There is thus a need to conduct ultrasound measurements of the cross-sectional area of nerves in the setting of CIPN.

Since most of our patients treated with platinum-based compounds were treated with oxaliplatin, some specific genomic changes can be used as an indicator of their specific nerve predilection. Results of a prospective and multicenter study have demonstrated that nucleotide polymorphism of voltage-gated sodium channels gene (SCN9A-rs2302237) is a predictive factor for the severity of acute polyneuropathy. Also, the presence of other single-nucleotide polymorphisms makes it possible to predict the severity of polyneuropathy in patients treated with oxaliplatin [42,43]. There is still a need to link specific genotype to particular clinical symptoms or signs and to specific electrophysiologic findings.

One limitation of this study was that the number of participants was small. Involving more patients, and systematic clinical and electrophysiological evaluation of patients to be treated with chemotherapy, would have given more comprehensive data about peripheral nervous system involvement. Using quantitative sensory testing could have been an additional tool in evaluation of small fiber involvement in CIPN.

Conclusions

The findings supported previous studies and showed that CIPN, including sensory and motor symptoms, was commonly associated with chemotherapy. Platinum-based chemotherapy agents were more commonly associated with ulnar and tibial nerve damage in this study population.

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