Burden of Chemotherapy-Induced Neuropathy in School ged children

M. D, Artan Shkoza
University of Medicine, Tirana, Albania
Msc., Mirlinda Likmeta
University of Medicine, Tirana, Albania
M. D, PhD, Ledjan Malaj
University of Medicine, Tirana, Albania

Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is the most common neurological complication in cancer treatment and probably the most common toxic neuropathy in our environment. The aim of the study was to assess the incidence and discomfort caused by neuropathic symptoms in children treated for hematologic cancers. The study included all children admitted to the pediatric oncology service at the University Hospital Center "Mother Teresa", Tirana, by the year 2011 – 2013 divided in three diagnosis groups: acute lymphoblastic leukemia, Hodgkin and non-Hodgkin's lymphoma, or other solid tumors. In a prospective cohort setting, data were collected by standard questionnaire for symptoms and signs of neurological damage, according to The Pediatric - Modified Total Neuropathy Scale (Ped - mTNS), as well as clinical evaluation of pin sensibility, vibration sensibility, muscle strength and deep tendon reflexes (DTR). The results obtained from Ped-mTNS, showed the high incidence of sensory and motor symptoms as well as functional deficits in balance and manual dexterity in children treated with anticancer drugs. Ped-mTNS scores, as the first measure designed to assess CIPN in school-aged children, are significantly higher for children undergoing neurotoxic chemotherapy. Even though the neuropathy in these children was relatively mild, it was associated with functional deficits in balance and manual dexterity, suggesting clinical importance. An important limiting factor of this study is the exclusion of children younger than 5 years old, whom discomfort is evident but not properly evaluated.

Keywords: Peripheral neuropathy, chemotherapy, toxicity in children.

Introduction

Many pediatric cancer diagnoses now have 5-year survival rates of over 85 % due to the use of multimodal treatment that often includes chemotherapy (Ries et al., 1999, 99). Unfortunately, a number of chemotherapeutic medications have potential long term effects, including neurotoxicity. In the peripheral nervous system (PNS), this toxicity often manifests as chemotherapy-induced peripheral neuropathy (CIPN); while in the central nervous system, toxicities range from cognitive and intellectual impairments to encephalopathy and coma.

Symptoms of neurotoxicity in the PNS are often under-recognized and undiagnosed in adult patients (Markman, 2006, 275). Even less is known about the prevalence and impact of CIPN in pediatrics. One major reason for sparse data has been the lack of specific and sensitive measurement tools for CIPN in the pediatric population. The most neurotoxic chemotherapeutic agents are vinca alkaloids, cisplatin and its

derivatives and taxanes (Quasthoff & Hartung, 2002, 9).
The first early sensory symptoms are paresthesias and numbness, which occur usually between the first and third cycles of therapy. Motor weakness usually develops later, because sensory neurons and axons that transmit pain perception are unmyelinated and lightly myelinated fibers and are more susceptible than motor fibers to toxic damage.
Sensory symptoms may persist or even develop weeks to months after discontinuation of the chemotherapy. This feature, known as "coasting," was first detected with the vinca alkaloid vincristine. Sensory loss refers to pin, touch, or both. It is due to the distal degeneration of sensory axons (Krarup-Hansen, Helweg-Larsen, et al., 2007, 1076). The neuronal injury begins at the most distal portion of an axon where the lack of nutritional cytoplasmic support is more pronounced (Asbury, 1987, 58).
Neuropathic pain is prominent and important for many patients, and its severity may be dose-limiting, particularly in the treatment of multiple myeloma with bortezomib (Cavaletti & Nobile-Orazio, 2007, 1308). Additionally, patients with pre-existing neuropathies of any kind (eg, diabetic, paraneoplastic, alcoholic, or hereditary) show an increased propensity to develop neuropathy when treated with neurotoxic agents used in cancer treatment (Chaudhry et al., 2003, 337 & Graf et al., 1996, 1356). CIPN is less frequent and severe with second-generation vinca alkaloids such as vinorelbine and vinflunine (Swain & Arezzo, 2008, 455).
At present, early detection and management of CIPN are the best approaches available to prevent its progression towards a severe and disabling neuropathy.

Materials and methods

The study included all children admitted to the pediatric oncology service at the University Hospital Center "Mother Teresa", Tirana, by the year 2011 - 2013 with a diagnosis of acute lymphoblastic leukemia, Hodgkin and non-Hodgkin's lymphoma, or other solid tumors. In a prospective cohort setting, data were gathered by standard questionnaire (Table 1) for symptoms and signs of neurological damage modified for children (*Pedm-TNS*), as well as clinical evaluation of light touch sensation, pin sensibility, vibration sensibility, muscle strength and deep tendon reflexes, prior and two to six month after chemotherapy treatment (Gilchrist, Tanner, Hooke, 2009, 7).

Table1. Pediatric - Modified Total Neuropathy Scale

Name_____**Surname**_____**Record number**_____
Sensory Symptoms:_____ (record worst score for the three sensations)
"Do you have any parts of your body that are tingly, numb (can hardly feel), or hurt?"
_____Tingly_____Numb_____Hurt (record number for each)
If yes, "Where you have those feelings?"
0 None
1 Symptoms limited to fingers or toes
2 Symptoms extend to ankles or wrists
3 Symptoms extend to knee or elbow
4 Symptoms above knee or elbow

Functional Symptoms (motor): _____ (record worst score of the three questions)"
"Do you have trouble buttoning shirts or zipping zippers?" _____
"Do you have trouble walking such as tripping frequently?" _____
"Do you have trouble going up or down stairs?" _____
If yes to any, "Is it…..(read choices)" and record after each question:

0 Not Difficult
1 A little difficult
2 Somewhat difficulty
3 I need help
4 I can't do that at all

Clinical Testing:
Light Touch Sensation: _____

0 Normal
1 Reduced in fingers/toes
2 Reduced up to wrist/ankle
3 Reduced up to elbow/knee
4 Reduce to above elbow/knee

Pin Sensibility:

0 Normal
1 Reduced in fingers/toes
2 Reduced up to wrist/ankle
3 Reduced up to elbow/knee
4 Reduced to above elbow/knee

Vibration Sensibility: _____ (worst score)

0 Normal
1 Reduced in fingers/toes
2 Reduced up to wrist/ankle
3 Reduced up to elbow/knee
4 Reduce to above elbow/knee

Muscle Strength: ____ Worst Score :

MRC level: Great Toe __/__ ankle DF__/__ finger abd___/___ wrist ext___/___

0 Normal
1 Mild weakness (MRC 4)
2 Moderate weakness (MRC 3)
3 Severe weakness (MRC 2)
4 Paralysis (MRC 1-0)

Deep Tendon Reflexes (DTR): ____ (Achilles, Patellar)

0 Normal
1 Ankle reflex reduced (Achilles +1)
2 Ankle reflex absent (Achilles 0, Patellar +2)
3 Ankle reflex absent, others reduced (Achilles 0, Patellar +1)
4 All reflexes absent (all 0)

Total Score:_____/28

Each category is rated from 0 to 4, with 0 indicating no symptom or deficit on clinical exam to 4 indicating worse symptoms or proximal spread of neurologic symptoms. The scale has 28 possible points (autonomic tests not included) and a higher score indicates worse neuropathy.

Results

The total number of patient admitted to the pediatric oncology service was 285**.** 114 of them were less than 5 years old and, did not meet inclusion criteria**.** Subject demographics are given in Table 2.

Table 2. Subject Demographics

Sex
- Male: 103/171 (60 %)
- Female: 68/171 (40 %)

Age
- Average ± SD: 9.3
- Range: 5-15

Diagnosis:
- Acute Lymphoblastic Leukemia: 93 (55 %)
- Lymphoma (Hodgkins and Non-Hodgkins): 33 (19 %)
- Solid Tumors: 45 (26 %)

Phase of Therapy:
- Intensive Therapy: 62 %
- Maintenance: 23 %
- Off therapy 2 months or less: 17 %

Main Neurotoxic Chemotherapic Agent:
- Vincristine: 88% (150/171)
- Cisplatin: 12% (21/171)

Descriptive statistics of scoring on the ped-mTNS are given in Table 3.

Table 3. Descriptive Statistics of Scoring on the ped-mTNS

Total Score (28 points possible) (n = 166)
- Mean ± SD: 6.4 ± 2.3
- Median: 6.0
- Range: 2 – 13

Score:
- 0 – 3 40 % (Nr. = 66)
- 4 – 9 35 % (Nr. = 58)
- 10+ 25 % (Nr. = 42)

Score ≥ 4:
- ALL: 54 % (50/93)
- Lymphoma: 45 % (15/33)
- Solid Tumor: 87 % (35/40)

Intensive therapy: 60 % (60/100)
Maintenance: 65 % (38/58)
Off Treatment < 2 mo: 25 % (2/8)

The detailed results obtained from standardized Ped-m TNS, showed the following:
60 % of children reported sensory symptoms, of whom 30 % (50/166) reported numbness, 30 % (50/166) tingling, 25 % (41/166) reported pain, and 20 % (33/166) reported numbness and tingling simultaneously.
52 % (86/166) of children reported motor symptoms, with all of these subjects reporting some difficulty with walking or ascending stairs.
28 % (46/166) showed impairments in pin sensibility, with a mean item score of 0.3 ± 0.5 and a range of 0-1, indicating that subjects had decreased pin sensibility only in their toes or fingers when impacted.
Four of children who could not participate in the study were found to have depressed nerve conduction studies.

Discussion

Chemotherapy- induced peripheral neuropathy (CIPN) is the most common neurological complication in cancer treatment (Kannarkat et al., 2007, 719). From the first reported case of sensory neuropathy secondary to cisplatin over 30 years ago (Kedar et al., 1978, 819), the problem of neurotoxicity in relation to these treatments has always been part of the oncology scene. Similar to the findings of Wampler et al. (Wampler et al., 2006, 9), even though the neuropathy in these children was relatively mild, it was associated with functional deficits in balance and manual dexterity, suggesting clinical importance.
The importance of CIPN lies in two factors: it impairs pateint's quality of life (Cavaletti at al., 1994, 1287 and Mileshkin at al., 2002) and it is a dose limiting factor (Wolf et al., 2008, 1507 and Mileshkin et al., 2006, 4507).
There are several strengths and limitations in this study. Strengths include the study design presenting real-life clinical practice. In the present study, the occurrence of neurotoxicity is in line with the previous literature confirming the reliability of the study (Lavoie Smith E, at. al, 2010). The strongest limitation of the present study is that we selected only patients treated with neurotoxic agents like vinca alkaloids, platinum and taxanes. Also, because of large variation in doses and duration of treatment, no comparisons between different chemotherapy regimens or analysis or dose response were feasible.
Another important limiting factor of this study is the exclusion of children younger than 5 years old.

Conclusions

The study gives new information of the inconvenience caused by neuropathic symptoms in a patient's point of view. Our finding is in line with previous literature that chemotherapy-induced neuropathy is a common adverse effect with low intensity. However, the intensity and inconvenience of the neuropathic symptoms does not correlate with each other. Neuropathic symptoms seem to be very troublesome even though the intensity of the symptoms is generally mild. This should be taken into account when planning and informing patients of neurotoxic chemotherapy. A more

serious concern is about children younger than five years old, who cannot understand physician questions and report their symptoms.

References

Ries, LAG., Smith, MA., Gurney, JG., et al., (1999). *Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995, National Cancer Institute, SEER Program*. NIH Pub. No. 99–4649. Bethesda, MD.

Markman, M. (2006). *Chemotherapy-induced peripheral neuropathy: underreported and underappreciated.* Curr Pain Headache Rep 10:275–278.

Quasthoff, S., Hartung, HP. (2002). *Chemotherapy-induced peripheral neuropathy*. J Neurol 249:9–17.

Krarup-Hansen, A., Helweg-Larsen, S., et al. (2007). *Neuronal involvement in cisplatin neuropathy: prospective clinical and neurophysiological studies*. *Brain*, **130:**1076–1088.

Asbury, AK. (1987). *Sensory neuronopathy*. *Sem Neurol*, **7:** 58–66.

Cavaletti G, Nobile-Orazio E (2007). *Bortezomib-induced peripheral neurotoxicity: still far from a painless gain*. Haematologica; 92 (10):1308–10.

Chaudhry, V., Chaudhry, M., Crawford, TO., et al., (2003). *Toxic neuropathy in patients with pre-existing neuropathy*. *Neurology*, **60**:337–340.

Graf, WD., Chance, PF., Lensch, MW., et al., (1996). *Severe vincristine neuropathy in Charcot-Marie-Tooth disease type 1A*. Cancer, **77:**1356–1362.

Swain, SM., Arezzo, JC. (2008). *Neuropathy associated with microtubule inhibitors: diagnosis, incidence, and management*. Clin Adv Hematol Oncol; 6 (6):455–67.

Gilchrist, LS., Tanner, L., Hooke, MC. (2009). *Measuring chemotherapy induced peripheral neuropathy in children: development of the PedmTNS and pilot study results*. Rehabil Oncol 27:7–15.

Kannarkat, G., Lasher, EE., Schiff, D. (2007). *Neurologic complications of chemotherapy agents*. Curr Opin Neurol.; 20:719-25.

Kedar, A., Cohen, ME., Freeman, AI. (1978). *Peripheral neuropathy as a complication of cis-dichlorodiammineplatinum (II) treatment: a case report*. Cancer Treat Rep.; 62:819-21.

Wampler, MA., Miaskowski, C., Hamel, K. et al., (2006). *The modified total neuropathy score: a clinically feasible and valid measure of taxane-induced peripheral neuropathy in women with breast cancer*. J Support Oncol 4:9–16.

Cavaletti, G., Bogliun., G, Marzorati, L., et al. (1994). Long*-term peripheral neurotoxicity of cisplatin in patients with successfully treated epithelial ovarian cancer.* Anticancer Res 14:1287–1292.

Mileshkin, L., Antil, Y., Rischin, D. (2002). *Management of complications of chemotherapy*. In: Gershenson DM, McGuire MP, Gore M et al., (eds) Gynaecologic cancer: controversies in management. Elsevier Science, Philadelphia, PA.

Wolf, S., Barton, D., Kottschade, L. et al., (2008). *Chemotherapy-induced neuropathy: prevention and treatment strategies*. Eur J Cancer 44:1507–1515.

Mileshkin, L., Stark, R., Day, B., et al., (2006). *Development of neuropathy in patients with myeloma treated with thalidomide: patterns of occurrence and the role of electrophysiologic monitoring*. J Clin Oncol 24:4507–4514.

Lavoie Smith, E., Cohen, JA., Pett, MA., Beck, SL. (2010). *The reliability and validity of a modified total neuropathy score-reduced and neuropathic pain severity items when used to measure chemotherapy-induced peripheral neuropathy in patients receiving taxanes and platinums*. Cancer Nurs 33:173–183.