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ORIGINAL ARTICLE

Antineoplastic agents exacerbating Charcot Marie Tooth disease: red flags to avoid permanent disability

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ABSTRACT

Background: Charcot Marie Tooth (CMT) disease is the most common form of hereditary neuropathy. Due to the high prevalence of mild and undiagnosed forms, patients with CMT disease may be exposed to severe neurotoxicity following the administration of neurotoxic chemotherapies. The aim of this report is to alert oncologists to the potential to precipitate severe irreversible peripheral neuropathies when administering neurotoxic compounds to undiagnosed CMT patients.

Material and methods: A retrospective research in the OncoNeuroTox database was performed (2010–2016), searching for patients with the diagnosis of chemotherapy-induced peripheral neuropathy (CIPN) and CMT disease. A comprehensive literature review for previously published cases was performed using the Pubmed and Cochrane databases (1972–2017).

Results: Among 428 patients with CIPN, we identified eight patients with concomitant CMT disease. Seven patients out of the eight had no previous diagnosis of CMT disease, although accurate familial history disclosed mild signs of peripheral neuropathy in five cases. Patients themselves had minor stigmata of long-standing peripheral damage. Patients received chemotherapy regimens based on vinca alkaloids, taxanes or a combination of vinca alkaloids and platinum compounds. In two cases, cumulative doses were below or equal to the expected neurotoxic threshold. Following chemotherapy administration, patients developed severe length-dependent sensory-motor deficits. Despite early drug discontinuation, most patients remained severely disabled.

Conclusion: A brief checklist to disclose long-standing signs of peripheral neuropathy could be helpful to detect patients with undiagnosed hereditary neuropathies who could be at risk of developing severe irreversible neurotoxicity following the administration of neurotoxic agents.

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Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a recognized side effect of several antineoplastic agents, including vinca alkaloids, taxanes and platin compounds. CIPN primarily affects the sensory nerves and shows prominent axonal features on electroneurography. Besides drug type and cumulative dose, the existence of underlying hereditary or acquired neuropathies is a major risk factor for the development of CIPN [1–3]. In patients with underlying conditions, CIPN is particularly severe, and neurological deficits may be irreversible despite early drug discontinuation.

Charcot Marie Tooth (CMT) disease is the most common hereditary neuropathy [4], with an estimated incidence of 1/2500 people in the general population [5]. CMT disease actually corresponds to a heterogeneous group of conditions that highly differ on electrophysiological [6] and genetic grounds [7]: demyelinating (CMT1), axonal (CMT2) and intermediate (CMTI) types of CMT disease have been reported, and each group has been associated with a different set of genetic alterations [4]. CMT usually manifests during childhood with cavus feet, weakness and numbness in lower limbs causing progressive gait disturbances. However, in many individuals, CMT disease is paucisymptomatic and remains undiagnosed throughout life. This observation suggests that the prevalence of CMT disease could be significantly higher than currently reported.

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CMT patients, who are unaware of their condition, are potentially exposed to severe CIPN following the administration of antineoplastic agents with neurotoxic properties. The aim of this report is to raise the attention of oncologists to the risk of exacerbating severe irreversible peripheral neuropathies in patients with undiagnosed CMT disease.

Patients and methods

We performed a retrospective research in the OncoNeuroTox database for the period 2010–2016, searching for patients with CIPN and CMT disease. OncoNeuroTox corresponds to a network of institutions to which are referred patients presenting neurological complications from oncological treatments from the Ile-de-France region (estimated population: 12 million inhabitants). Clinical records of patients with CIPN and CMT disease were reviewed in detail, with particular regard to infraclinical signs of hereditary peripheral neuropathy in the personal and in the family history, and the chemotherapy regimens they received for their oncological condition. Clinical severity was measured by the clinical version of the Total Neuropathy Score (TNSc), which has been validated as an accurate tool in the setting of CIPN [8]. Muscle strength was measured by the Medical Research Council (MRC) scale.

A comprehensive literature review in search for similar cases was also performed. The Pubmed and Cochrane databases were searched for the combinations of the following keywords: 'Charcot Marie Tooth', 'hereditary neuropathy', 'neurotoxicity', 'cancer', 'chemotherapy', 'vincristine', 'vinca alkaloids', 'taxanes' and 'platinum compounds'. All articles written in English, French, German, Spanish or Japanese, and published up to May 2017 (1972–2017) were included in this review.

Results

We identified 428 patients with CIPN in the OncoNeuroTox database. Eight of these patients (8/428 = 1.9%) had a concomitant diagnosis of CMT disease. The clinical and genetic features in our eight patients are detailed in Table 1.

Illustrative case (patient n°5)

A 32-year-old man underwent subtotal surgical resection in November 2008 for a right insular WHO grade II oligodendroglioma. The patient received 18 monthly cycles of temozolomide (200 mg/m^2/day for 5 days) followed by radiotherapy (60 Gy). In July 2013, he was started on PCV chemotherapy [Procarbazine 75 mg/m^2 on day 8–21; CCNU 130 mg/m^2 on day 1; Vincristine 1.4 mg/m^2 on day 8 and 29 (not exceeding the dose of 2 mg)] due to tumor progression. After the third cycle of PCV chemotherapy, the patient developed severe sensory-motor deficit in the upper and lower limbs, requiring bilateral support for walking. Neurological examination revealed severe tetraparesis, hypesthesia in a socking and glove distribution, areflexia and cavus feet. Electroneurography showed signs of chronic demyelinating neuropathy. Family history was positive for cavus feet in patient's maternal ascendants. Genetic analysis showed a duplication in the *PMP22 gene*, which is the most common genetic alteration detected in patients with CMT1 disease. Despite the prompt discontinuation of vincristine, the patient remained severely disabled. He ultimately died one year later because of tumor progression.

Case series

The eight patients in our series included three males and five females. Median age at the time of CIPN was 48.5 years (range 23–84). All patients had signs/symptoms in their personal and/or familial history evoking an underlying hereditary neuropathy including cavus feet, ankle retractions, or long-standing gait disturbances. However, only one patient (patient n° 2) had a genetically confirmed diagnosis of CMT1 before starting chemotherapy (this info was missing at that time for patient 7), while the other seven patients were referred to a neurologist (and diagnosed with CMT disease) only because of the acute clinical deterioration that followed chemotherapy administration.

Cancer type corresponded to breast carcinoma (4 patients), Hodgkin lymphoma (1patient), non-Hodgkin lymphoma (1 patient), oligodendroglioma (1 patient) and parotid carcinoma (1 patient). All patients received chemotherapy regimens based on neurotoxic compounds, including taxanes (3 patients) and vinca alkaloids (5 patients), either alone or in combination with platinum compounds. Although most patients received high cumulative doses, two patients developed CIPN for cumulative doses below (or equal to) the neurotoxic threshold (patients n°5 and n°7).

Chemotherapy administration triggered acute neurological deterioration resulting in major disability: at the peak of disease severity, two patients were bedridden and the remaining five could walk only with uni- or bilateral support (median TNSc 15; range 9–22). CIPN was characterized by length-dependent sensory-motor deficits in all cases, affecting the four limbs in seven out of the eight patients (88%). Motor deficits prevailed in distal muscles and ranged from mild (MRC 4) to severe (MRC <2) impairment. Sensory symptoms included distal numbness and paresthesia; two patients had severe neuropathic pain, which, however, was never reported as the initial symptom. None of the patients had autonomic dysfunction. One patient, who was severely affected, developed respiratory failure due to diaphragmatic involvement (patient n° 7).

Electroneurography confirmed a moderate to severe sensory-motor neuropathy in all cases, with either demyelinating (5 cases; patients n° 2, 4, 5, 6, 7) or axonal (3 cases; patients n° 1, 3, 8) features. In all cases, a comprehensive work-up was performed to exclude concomitant conditions responsible for acquired peripheral neuropathies (vitamin B12/folate deficiency, diabetes, thyroid disease, autoimmune disorders, uremia, hepatitis B, hepatitis C, HIV infection and Lyme disease). Genetic testing was decided on electroneurographic features and supposed mechanism of heritance. Genetic alterations commonly involved in CMT disease were

Table 1. Clinical and genetic characteristics in our eight patients.

Pt	Age/ Gender	Signs/symptoms of hereditary neuropathy in the family	Cancer type	Chemotherapy (cumulative dose)	Threshold for neurotoxicity [3]	Delay from chemotherapy administration to acute neurological deterioration	Signs/symptoms of pre-existing neuropathy	Neurological impairment following chemotherapy administration	TNSc[a] at the peak of disease severity	Final diagnosis	Genetic alteration	TNSc[a] at last FU	Patient status at last FU
1	48/F	Gait disturbance (father)	Breast Grade n.a	Docetaxel (672 mg)	>100 mg/m^2	n.a	Cavus feet Cramps Scoliosis	Lower limbs impairment: Severe distal motor deficit (MRC 2) Neuropathic pain and distal paresthesia Areflexia	14	CMT1B Axonal type	*MPZ c.233C > T (p. Leu78Ser)*	14	no recovery; walks with unilateral support
2	46/F	Genetically confirmed diagnosis of CMT1 in the family	Breast Grade IV	Vinorelbine (336 mg)	Unknown	3 months	Cavus feet Gait disturbance Mild distal motor deficit	Four limbs impairment: Moderate to severe distal motor deficit (MRC 2–3) Distal hypesthesia Areflexia	16	CMT1A Demyelinating type	Dup *PMP22*	14	minor recovery; walks without aid
3	84/F	Scoliosis (aunt) Cavus feet (daughter)	Breast Grade IV	Paclitaxel (2340 mg)	>300 mg/m^2	4 months	Ankle retractions Cavus feet Scoliosis	Four limbs impairment: Moderate distal motor deficit (MRC 3) Severe distal paresthesia Areflexia	12	CMT Axonal type	No mutation found (*MFN2, PO, CX 32, GDAP1*)	12	no recovery; walks with unilateral support
4	52/M	Not reported	Parotid Grade III	Cisplatine (480 mg) Vinorelbine (351 mg)	>350 mg/m^2 unknown	2 months	Cavus feet Ankle retractions Calf atrophy	Four limbs impairment: Mild motor deficit (MRC 4) Paresthesia Areflexia	15	CMT1A Demyelinating type	Dup *PMP22*	13	minor recovery; walks without aid
5	32/M	Per Cavus (mother)	Oligodendroglioma	Vincristine (6 mg)	>2–6 mg/m^2	1 month	Cavus feet	Four limbs impairment: Moderate to severe tetraparesis (MRC 2-3) Distal hypesthesia Areflexia	17	CMT1A Demyelinating type	Dup *PMP22*	15	minor recovery; walks with bilateral support
6	52/F	Gait disturbance (father)	Breast Grade IIIA	Paclitaxel (672 mg)	>300 mg/m^2	n.a	Gait disturbance Cavus feet Scoliosis	Four limbs impairment: Moderate motor deficit Severe pain and distal paresthesia Areflexia	n.a.	CMT4C Demyelinating type	*SH3TC2 c.150_1523delTTGT (p.Phe507rpfsX16 c.2860C > T p.Arg954X)*	18	partial recovery; walks with unilateral support
7	23/M	CMT disease in the family (sister)	NHL Grade IV	Vincristine (4 mg)	>2–6 mg/m^2	2 months	Cavus feet	Four limbs impairment: Tetraplegia (MRC <2) Respiratory failure	22	CMT1A Demyelinating type	Dup *PMP22*	17	partial recovery; walks without aid
8	48/M	Cavus feet (two cousins)	HL Grade IVB	Vincristine (12 mg)	>2–6 mg/m^2	2 months	Cavus feet Scoliosis	Four limbs impairment: Mild distal motor deficit (MRC 4) Distal hypesthesia Areflexia	9	CMT Axonal type	No mutation found (MFN2, PO, CX 32, GDAP1)	9	no recovery; walks without aid

CMT: Charcot Marie Tooth; Dup: duplication; F: female; FU: follow-up; HL: Hodgkin Lymphoma; M: male; MRC: Medical Research Council; n.a: not available; NHL: Non-Hodgkin Lymphoma; Pt: patient.
[a]TNSc ranges from a minimum of 0 (no signs or symptoms of disease) to a maximum of 24 (paralysis requiring help/assistance, functionally disabling sensory symptoms, reduced pin and vibration sensibility, absence of reflexes).

Table 2. Review of the clinical features in the 38 patients with CIPN and CMT identified in literature.

Pt	Age	Gender	Diagnosis of CMT in the family	Signs/symptoms of hereditary neuropathy in the family	Cancer	Chemotherapy (cumulative dose)	Signs/symptoms of pre-existing neuropathy	Neurological impairment following chemotherapy administration	CMT type (genetic alteration)	Outcome of the CIPN	Ref.
1	46	M	No	Cavus feet Distal weakness (father, brother)	Embrional- cell carcinoma of the testes	Vincristine (4 mg)	Cavus feet Distal weakness	Tetraparesis Paresthesia Bulbar dysfunction Diaphragm palsy Areflexia	CMT1 (dup *PMP22*)	Death (respiratory failure)	[9]
2	2	M	No	Cavus feet Distal LL weakness (mother, grandfather)	ALL	Vincristine (3.5 mg)	No	Tetraparesis Areflexia	CMT1	Partial recovery	[10]
3	12	F	Yes	Thenar atrophy Areflexia (father)	ALL	Vincristine [1.8 mg/m^2(4 cycles)]	Cavus feet	Tetraparesis Facial palsy Bulbar dysfunction	Not reported	Partial recovery Died one year later (cancer relapse)	[11]
4	57	F	Yes	Not reported	NHL	Vincristine (2 mg)	Not reported	Severe motor deficit	Not reported	Partial recovery	[12]
5	60	M	No	Cavus feet (father, brother, niece)	MM	Vincristine (2 mg)	Cavus feet	Distal weakness and paresthesia Areflexia	Not reported	Partial recovery	[13]
6	14	M	Yes	Not reported	HL	Vincristine (4 mg)	Scoliosis	Distal weakness and paresthesia Areflexia	CMT1	Partial recovery	[14]
7	33	F	Yes	Not reported	HL	Vincristine (4 mg)	Not reported	Distal weakness and hypesthesia Bulbar dysfunction Hyporeflexia	CMT1	Partial recovery	[14]
8	9	F	Yes	Distal weakness (aunt)	ALL	Vincristine (1.5 mg/m^2)	No	Tetraparesis Distal hypesthesia Areflexia	CMT1 (dup *PMP22*)	Partial recovery Died 11 months later (cancer relapse)	[15]
9	18	F	Yes	Hammer toes Areflexia (sister, mother, grandmother)	Burkitt lymphoma	Vincristine (1.4 mg/m^2)	Cavus feet	Distal weakness and hypesthesia Areflexia	CMT1 (dup *PMP22*)	Partial recovery	[15]
10	5	M	No	Gait disturbance (father, brother)	NHL	Vincristine [1.5 mg/m^2 (1 cycle), 1.125 mg/m^2 (2 cycles)]	Distal hypesthesia Calf atrophy	Tetraparesis Neuropathic pain Areflexia	CMT1	Complete recovery	[16]
11	31	F	No	Gait disturbance (grandmother)	HL	Vincristine (2 mg)	Cavus feet Ankle retraction	Distal weakness Areflexia	CMT1 (dup *PMP22*)	Not reported	[17]
12	52	F	No	Paresthesia (mother) Feet deformities (grandmother)	NHL	Vincristine (4 mg)	Cavus feet	Distal weakness and paresthesia	CMT1 (dup *PMP22*)	Complete recovery	[18]
13	5	M	No	Not reported	ALL	Vincristine	No	Distal weakness Bulbar dysfunction Areflexia	CMT1 (dup *PMP22*)	Partial recovery	[19]
14	44	M	No	Not reported	NHL	Vincristine	Cavus feet	Tetraparesis Bulbar dysfunction	CMT1 (dup *PMP22*)	Partial recovery	[20]
15	5	M	No	Distal weakness (mother)	ALL	Vincristine	No	Tetraparesis Facial palsy Areflexia	CMT1	Partial recovery	[21]

(*continued*)

Table 2. Continued

Pt	Age	Gender	Diagnosis of CMT in the family	Signs/symptoms of hereditary neuropathy in the family	Cancer	Chemotherapy (cumulative dose)	Signs/symptoms of pre-existing neuropathy	Neurological impairment following chemotherapy administration	CMT type (genetic alteration)	Outcome of the CIPN	Ref.
16	16	M	No	Distal weakness (father)	Ewing sarcoma	Vincristine (2 mg)	No	Distal weakness and hypesthesia Areflexia	CMT1	Stable	[22]
17	5	M	Yes	Not reported	ALL	Vincristine [1.5 mg/m^2 (3 cycles), 0.75 mg/m^2 (1 cycle)]	No	Distal UL weakness Proximal LL weakness	CMT1 (dup *PMP22*)	Complete recovery	[23]
18	4	M	Not reported	Not reported	ALL	Vincristine [1.5 mg/m^2 (4 cycles), 0.75mg/m^2 (4 cycles)]	Not reported	Distal weakness	CMT1 (dup *PMP22*)	Partial recovery	[23]
19	4	F	Not reported	Not reported	ALL	Vincristine [1.5mg/m^2 (10 cycles)]	Not reported	Motor deficit Areflexia	CMT2	Partial recovery	[23]
20	5	M	Not reported	Not reported	ALL	Vincristine [1.5mg/m^2 (6 cycles)]	Not reported	LL weakness	CMT1 (dup *PMP22*)	Complete recovery	[23]
21	15	M	No	No	ALL	Vincristine [1.5mg/m^2 (4 cycles)]	No	Tetraparesis Bulbar dysfunction	CMT1 (dup *PMP22*)	Partial recovery Died 8 months later (infection)	[23]
22	55	M	No	No	LNH	Vincristine (4 mg)	Cavus feet Hammertoes	Distal weakness and paresthesia LL areflexia	CMT1	Partial recovery	[24]
23	16	F	No	No	Ewing sarcoma	Vincristine (6 mg)	Cavus feet	Distal weakness and paresthesia Areflexia	CMT1	Partial recovery Died 18 months later (cancer relapse)	[25]
24	10	F	No	Cavus feet Foot drop (father, grandfather)	ALL	Vincristine (6 mg)	Cavus feet	Distal weakness	CMT2	Partial recovery	[25]
25	32	F	No	Distal LL weakness Hyporeflexia (brother, mother, grandfather)	HL	Vincristine (2 mg)	Cavus feet	Tetraparesis and distal paresthesia Bulbar dysfunction Areflexia	CMT1	Partial recovery	[26]
26	28	M	No	Distal LL weakness Hyporeflexia (sister, mother, grandfather)	HL	Vincristine (7.5 mg)	No	Tetraparesis Neuropathic pain Areflexia	CMT1	Partial recovery	[26]
27	10	F	No	Not reported	Wilms tumor	Vincristine [1.5 mg/m^2 (4 cycles)]	No	Tetraparesis Hypoesthesia Hyporeflexia	CMT1 (dup *PMP22*)	Partial recovery	[27]
28	47	F	Not reported	Not reported	Breast	Vincristine (5 mg)	Distal LL weakness and hypesthesia	Tetraparesis Areflexia	CMT1	Not reported	[28]
29	17	F	No	Not reported	HL	Vincristine (2 mg)	No	Tetraparesis Areflexia	CMT1 (dup *PMP22*)	Partial recovery	[29]
30	13	M	No	No	ALL	Vincristine (8 mg)	No	Distal weakness (LL > UL)	CMT2	Complete recovery	[30]

(*continued*)

Table 2. Continued

Pt	Age	Gender	Diagnosis of CMT in the family	Signs/symptoms of hereditary neuropathy in the family	Cancer	Chemotherapy (cumulative dose)	Signs/symptoms of pre-existing neuropathy	Neurological impairment following chemotherapy administration	CMT type (genetic alteration)	Outcome of the CIPN	Ref.
31	5	M	Not reported	Not reported	ALL	Vincristine [1.5 mg/m^2 (6 cycles)]	No	Distal LL weakness Areflexia	CMTX *(Cx32)*	Complete recovery	[31]
32	11	F	No	No	ALL	Vincristine [1.5 mg/m^2 (4 cycles)]	No	Distal weakness Areflexia	CMT1 (dup *PMP22*)	Partial recovery	[32]
33	23	F	No	No	NHL	Vincristine (3.9 mg)	No	Distal weakness and paresthesia Neuropathic pain Areflexia	CMT1 (*EGR2*, p.Arg353Gly)	Partial recovery	[33]
34	5	F	Yes	Not reported	Wilms tumor	Vincristine [1.5 mg/m^2 (27 cycles)]	No	LL areflexia	CMTX *(GJB1, Arg164Gln)*	Stable	[34]
35	60	F	Not reported	Not reported	Ovary	Paclitaxel + Carboplatin	Weakness in LL	Distal weakness Gait disturbance	Not reported	Complete recovery	[35]
36	53	M	Not reported	Not reported	Testicular	Cisplatin [20mg/m^2(2 cyces)]	Cavus feet	Tetraparesis Distal paresthesia	CMT1 (dup *PMP22*)	Stable	[36]
37	23	M	Yes	Not reported	Osteosarcoma	Cisplatin [100mg/m^2 (7 cycles)]	Cavus feet Distal weakness and paresthesia	Unchanged compared to baseline	CMTX (*GJB1*, Arg164Gln)	Stable	[37]
38	16	F	No	No	Medullobla-stoma	Vincristine (2 mg)	No	Tetraplegia Bulbar dysfunction	CMT1 (dup *PMP22*)	Partial recovery Died 5 months later (cancer relapse)	[38]

ALL: acute lymphocytic leukemia; CIPN: chemotherapy-induced peripheral neuropathy; CMT: Charcot Marie Tooth; CMT1: Charcot Marie Tooth 1, demyelinating type; CMT2: Charcot Marie Tooth 2, axonal type; CMT I: Charcot Marie Tooth, intermediate type (axonal-demyelinating); dup: duplication; HL: Hodgkin lymphoma; LL: Lower Limbs; MM: Multiple Myeloma; NHL: Non-Hodgkin Lymphoma; Ref: reference; UL: Upper Limbs.

Table 3. Self-reporting checklist to raise the Suspicion of UN diagnosed CMT disease (SUN CMT questionnaire).

Have you had (or do you still have)?		
1.	Cavus feet or other feet deformity, including hammer toes	☐
2.	Calf atrophy	☐
3.	Frequent falls since childhood or difficulties in running or jumping that prevented you to perform sports	☐
4.	Weakness in lower limbs affecting your ability to walk	☐
5.	Long-standing numbness or paresthesia in lower and/or upper limbs	☐
6.	Frequent ankle sprains	☐
7.	Scoliosis needing arthrodesis or brace	☐
Has any of your blood relatives had one or more of these complaints?		
8.	Yes	☐

identified in all five patients with the demyelinating type [duplication in the *PMP22* gene (4 cases), heterozygote mutations in the *SH3TC2* gene (1 case)] and in one out of the three patients with the axonal type (missense mutation in the *MPZ* gene).

The occurrence of CIPN prompted in all cases the discontinuation of the compound involved in acute toxicity. Despite drug discontinuation, four patients remained moderately to severely disabled, requiring uni- or bilateral support for walking. Median TNSc at last follow-up was 14.5 (range 9-18). Six patients (patients n° 2, 3, 5–8) resumed chemotherapy using drugs with less (or no) neurotoxic properties (e.g., capecitabine, CCNU, cyclophosphamide) without displaying further neurological toxicity.

Literature review

Literature reports 38 cases of CIPN in patients with CMT, including 22 children and 16 adults (Table 2) [9–38]. Although only nine patients had a genetically-confirmed family history of CMT, eleven other patients had undiagnosed relatives with infraclinical signs of hereditary neuropathy. Almost half of patients (16/33, when information were reported) have neurological signs reflecting long-standing neuropathy such as calf atrophy, cavus feet or feet deformities. Vincristine was the antineoplastic agent primarily responsible for acute toxicity (92%). Importantly, the cumulative doses of vincristine were below the neurotoxic threshold (2–6 mg/m^2 [3]) in half of the cases. CIPN was generally characterized by length-dependent motor and/or sensory deficits involving the lower and/or the upper limbs. Bulbar dysfunction (21%) and facial palsy (5%) were reported in a minority of cases. One patient (3%) developed diaphragmatic involvement which caused respiratory failure and death [9]. Although limited data are available about long-term outcome, most patients showed incomplete recovery and were left with permanent sequelae.

Discussion

This series describes eight patients with CMT disease who developed acute severe sensory-motor deficits following the administration of neurotoxic chemotherapies. None of the patients (except for one) had a previous diagnosis of CMT disease, and the hereditary neuropathy was diagnosed only after severe irreversible chemotherapy-induced neurotoxicity had occurred. Clinical presentation was characterized by severe sensory-motor impairment in lower and upper limbs, possible bulbar dysfunction and, in one case, by respiratory failure due to diaphragmatic involvement. CIPN was associated with permanent sequelae in all patients in our series, as none of them returned to their baseline status.

As outlined, CIPN in patients with CMT disease is characterized by clinical features that differ from the phenotype commonly observed in normal individuals. However, the real challenge is to identify infraclinical signs of CMT disease before administering neurotoxic agents, in order to spare patients with CMT disease from the severe and irreversible consequences associated with the administration of these compounds. Vincristine is the drug that has been most frequently associated with CIPN in patients with CMT disease, so that it is now contraindicated in patients with CMT disease [39]. Here, we propose a simple self-reporting checklist, which could be useful to disclose signs of undiagnosed CMT disease in patients candidates to receive vincristine (Table 3). In the presence of three or more positive answers, the referral to a neurologist for a complementary evaluation should be considered. Whenever in doubt, a mutidisciplinary evaluation may be avised to weigh the risk and benefits, in order not expose the patient to permanent sequelae, but neither delay antitumoral treatment or deprive the patient of precious treatment options in the fear of toxicity. Although the reported incidence of CMT in the general population may appear insufficient to justify this screening procedure, the observation that the prevalence of CMT disease may be substantially underestimated, together with the reports of life-threatening toxicity following vincristine administration in CMT patients, could be worth this quick and simple procedure. The need to find effective strategies to prevent these events is highlighted by the risk of permanent sequelae: patients may be severely disabled and prevented from working lifelong, resulting in a substantial burden for the patient himself, his family and society (especially when considering children and young adults).

Indeed, a major question is how to proceed in cancer care after acute neurotoxicity has occurred. Whenever possible, the agent responsible for acute toxicity should be abandoned in favor of a less neurotoxic compound. In all cases, however, a close neurological follow-up should be established in order to monitor the patient for clinical and

electrophysiological signs of peripheral nerve conduction deterioration.

Little is known about the mechanism responsible for precipitating severe acute toxicity in CMT patients following the administration of vincristine or other neurotoxic compounds. Indeed, some studies suggest that certain genetic variants associated with CMT disease may increase the risk for CIPN [40,41], accounting for the observation that CMT patients may develop this complication for cumulative doses below the established neurotoxic threshold.

In conclusion, CIPN is a recognized side effect of several chemotherapeutic agents. Although CMT disease is considered a rare condition, the consequences of administering neurotoxic compounds such as vincristine to patients with this condition can be severe and irreversible. Effective strategies to screen and identify patients potentially bearing hereditary neuropathies are needed to prevent undiagnosed CMT patients from developing these disabling and potentially life-threatening complications.

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