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ORIGINAL ARTICLE

Prevention, diagnosis and management of chemotherapy-induced peripheral neuropathy: a cross-sectional study of French oncologists' professional practices

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Abstract

Purpose Chemotherapy-induced peripheral neuropathy (CIPN) is challenging for oncologists. Many publications mention the high incidence of CIPN and the lack of effective preventive/management strategies and robust diagnostic tools. This cross-sectional study was aimed at assessing the practice of French oncologists for CIPN prevention, diagnosis and management.

Methods This web-based survey was sent to French oncologists by the regional cancer networks. Incidence and impact of CIPN were assessed using visual analogue scales (VAS) and diagnostic strategies were recorded. Also recorded were the drugs used to prevent or manage CIPN and their perceived efficacy and safety (VAS).

Results Among the 210 oncologists included, the perceived incidence of CIPN was about 36.2 ± 22.1% of patients. About 99.5% of oncologists declared that they assess CIPN during medical follow-up. The use of drugs to prevent CIPN was reported by 9.6% of oncologists (group B vitamins (35.0%) and calcium and magnesium infusion (25.0%)). In the case of CIPN, the therapeutic adjustment of neurotoxic anticancer drugs is performed by 99.0% of oncologists (chemotherapy change (49.8%), dose reduction (30.9%) or interruption (19.3%)). The pharmacological management of CIPN was declared by 72.9% of oncologists. The main drugs used are pregabalin (75.8%), amitriptyline (32.7%) and gabapentin (25.5%). Duloxetine (ASCO recommendation) is used by only 11.8% of oncologists.

Conclusion Oncologists were clearly aware of CIPN risks, but its incidence tended to be underestimated and the ASCO recommendations for the management of CIPN were not followed. The prevention, diagnosis and management of CIPN remain problematic in clinical practice in France.

Trial registration ClinicalTrials.gov: NCT03854864

Keywords Chemotherapy-induced peripheral neuropathy · Cancer · Adverse drug reaction · Oncologists · Professional practice

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Introduction

Several anticancer drugs are responsible for chemotherapy-induced peripheral neuropathy (CIPN), such as platinum-based anticancer drugs (e.g. cisplatin, oxaliplatin), proteasome/angiogenesis inhibitors (bortezomib, thalidomide), vinca alkaloids (e.g. vincristine) and taxanes (e.g. paclitaxel, docetaxel). These neurotoxic anticancer drugs are used in first-line chemotherapy for several and mostly prevalent cancers, including colorectal, breast and lung cancers, and multiple myeloma [1]. Symptoms of CIPN have a common "stocking and glove" distribution characterized by paraesthesia, dysesthesia, numbness and tingling, sometimes associated with neuropathic pain [2, 3]. The overall incidence of CIPN during chemotherapy treatment is estimated at approximately 48–52.7% (possibly up to 90% of patients treated with oxaliplatin during chemotherapy) [1, 4–6]. The long-term reversibility of CIPN remains questionable, notably in the case of platinum-based anticancer drugs and taxanes, and it may last several years after the end of chemotherapy [1]. CIPN has a deleterious effect on patients' quality of life (QoL) and leads to comorbidities such as psychological distress, fall risks and sleep disorders [7, 8]. Moreover, CIPN affects a specific population of patients already impacted by cancer, which is a strong driver of a decline in physical functioning and increased risk of depression in older adults [9]. According to the American Society of Clinical Oncology (ASCO), no agent is recommended for the prevention of CIPN. As for its treatment, available data indicates only a moderate recommendation for duloxetine [10, 11]. Thus, available and validated strategies are very limited and oncologists are frequently obliged to decrease or stop neurotoxic anticancer drugs, with a possible deleterious impact on the oncological prognostic [12].

In addition to the clinical impact of CIPN and treatment difficulties, the diagnosis of CIPN is also a source of concern. The diagnosis of CIPN is not standardized, as shown in the systematic review/meta-analysis of Seretny et al. [4]. Among the 31 studies included, their authors used 5 different methods of assessment alone or in combination, including the Common Terminology Criteria for Adverse Events from the National Cancer Institute (NCI-CTCAE), the Total Neuropathy Score, the core QoL questionnaire from the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30) and neuro-physiological examinations (nerve conduction studies, quantitative sensory testing and neurological examination) [4]. More specific questionnaires have been developed such as the Functional Assessment of Cancer Therapy–Taxane and the QLQ-CIPN20 (EORTC) [13]. No gold standard for the diagnosis of CIPN has been defined to this date. The incidence and severity of CIPN is frequently underreported by patients and underassessed by clinicians [14]. It has been suggested that the best method of assessment would be to associate clinician- and patient-reported outcome measures (e.g. NCI-CTCAE and QLQ-CIPN20) [15]. Consequently, consensus is needed to standardize assessment and diagnosis, notably for routine care activity [13].

The lack of diagnostic standardization associated with the paucity of effective treatments could contribute to a lack of CIPN management. Very few studies are available on the real-life management of CIPN by oncologists. It is however essential to know their screening and treatment practices. The objective of this study was to assess the current practices of CIPN diagnosis, prevention and management implemented by French oncologists in 2019.

Materials and methods

Study design

This multicentre, online and cross-sectional study was designed to assess the current practice of CIPN diagnosis, prevention and management by French oncologists.

The primary objective was the assessment of management strategies used by oncologists to treat CIPN. The secondary objective was to assess the preventive strategies used to limit it. The perceived efficacy and safety of drugs used to manage or prevent CIPN were recorded. Furthermore, the perceived incidence of CIPN and the diagnostic methods used by oncologists were assessed.

The study was designed to conform to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for reporting observational studies [16]. The study protocol was registered on the ClinicalTrials.gov website NCT03854864. The study was anonymous and approved by an ethics committee (No.2019/CE08, 18/02/2019, IRB: 00008526). Consent was obtained by the answer to the survey.

Setting

This study was coordinated and sponsored by the University Hospital of Clermont-Ferrand (CHU Clermont-Ferrand). All the oncologists were recruited in 11 French regions (Auvergne-Rhône-Alpes, Bourgogne-Franche-Comté, Bretagne, Centre-Val de Loire, Grand Est, Ile de France, Normandie, Nouvelle-Aquitaine, Occitanie, Pays de la Loire, Provence-Alpes-Côte d'Azur-Corse-Monaco) thanks to the French cancer regional networks. The inclusion of oncologists and data collection were done from January 14 to March 26, 2019.

Participants

To be included in the study, participants had to be oncologists (physician or surgeon) and prescribe neurotoxic anticancer drugs. Pain physicians could not be included in the study.

Oncologists were contacted by email from the mailing lists of the regional cancer networks. Emails were resent every 2 weeks during the study period. The emails sent included the description of the study objectives and a link to the online survey (supplementary file). The answer to the survey was given online with no longitudinal follow-up.

Variables

The primary endpoint was the use of management strategies (yes/no) and the name of the drug used among a list of analgesic and antineuropathic medications.

The secondary endpoints included the use of preventive strategies (yes/no) and the name of the drug used among a list of analgesic and antineuropathic medications. The perceived efficacy and safety of these management and preventive strategies were assessed with visual analogue scales (efficacy VAS: 0 no efficacy–100 maximal efficacy; safety VAS: 0 acceptable adverse effects–100 unacceptable adverse effects).

Before chemotherapy prescription, oncologists were asked if they discuss of CIPN risk with patients (yes/no) and do therapeutic adjustments in case of neuropathy risk factors (dose reduction/protocol change/no). In case of CIPN onset, oncologists were asked if they do therapeutic adjustments (dose reduction/discontinuation of the neurotoxic anticancer drug/protocol change/no); perceive that a therapeutic adjustment has a negative impact on patients' survival (yes/no); and transfer the patient to a pain physician (yes/no). The incidence of CIPN was estimated by a VAS of the percentage of patients developing CIPN (0–100%) and analysed as a continuous variable. The consequences of CIPN on patients' health-related QoL were assessed with a VAS (0 no consequence–100 very important consequences). Oncologists were also asked if they assessed CIPN during chemotherapy (systematically/at patient demand/no) and the methods of CIPN assessment (questionnaires, clinical exams and neurologic opinion).

The characteristics of oncologists were also recorded, including age, gender, physician/surgeon, organ/system specialty, estimated number of annual chemotherapy prescriptions, type of prescribed neurotoxic anticancer drugs and type of workplace (university hospital, general hospital, cancer centre and private hospital).

Data sources/measurement

All the data were obtained from the answer to the online survey. All the data were recorded and managed using REDCap electronic data capture tools hosted by the sponsor [17].

Bias

The study was sent to oncologists by email by the French cancer regional network in order to avoid a bias selection. The questionnaire was designed to be as short as possible to avoid missing data.

Sample size estimation

The primary objective was exploratory, aiming at the assessment of the therapeutic strategies used by oncologists to treat CIPN. Also, sample size calculation was performed to estimate the mean of the continuous CIPN outcome variable in a single population. By applying the following formula $((Z.\sigma)/E)^2$, with Z being the value obtained from the standard normal distribution reflecting the confidence level to be assigned (e.g. $Z = 1.96$ for 95%), σ the standard deviation of CIPN and E the desired margin of error, it was necessary to include at least 117 oncologists for an expected standard deviation ranging between 25 and 30 and a margin of error of 5%.

Furthermore, the sample size of around 120 oncologists allowed highlighting between-group differences with a standard deviation greater than 0.5 (i.e. effect size equals 0.5) for a two-sided type I error at 5% and a statistical power greater than 80%.

Statistics

The statistical analyses were performed using Stata software (version 15, StataCorp, College Station, USA). All the statistical tests were performed for a two-sided type I error at 5%, applying when necessary a correction to take into account multiple comparisons. Continuous variables were expressed according to their statistical distribution as mean and standard deviation or median and interquartile range. Concerning the paired comparisons such as comparisons of efficacies and safeties between used drugs, random effect models were run to take into account between- and within-oncologist variability (as random effect). For the efficacies of drugs, post hoc two-by-two comparisons have been done. A Sidak's type I correction was applied. Moreover, the relationships between continuous parameters were evaluated using Pearson or Spearman correlation coefficients, according to the statistical distribution of variables. The comparisons for continuous parameters were performed using the Student t test or Mann-Whitney test when the assumptions of the t test were not met. Homoscedasticity was assessed by using the Fisher-Snedecor test. The results were expressed using Hedges' effect size (ES) and a 95% confidence interval. The interpretation was conducted according to Cohen's recommendations defining effect size bounds:

small (ES: 0.2), medium (ES: 0.5) and large (ES: 0.8) [18–20]. Many of these analyses could be considered exploratory. As reported in the literature [21–23], individual p values have been reported without applying systematically mathematical correction but with a specific attention to the magnitude of differences (i.e. ES). As less than 5% missing data was observed for the main parameters, no imputation approach was applied.

Results

Characteristics of oncologists

Two hundred sixteen questionnaires were filled in with the online survey system (mean response rate per centre: 12.5%) and 210 answers were included in the analysis (Fig. 1). The characteristics of the participating oncologists are detailed in Table 1. The main profile of oncologists was medical oncologists (93.8%) and working in general hospitals (43.8%). The oncological specialties most represented were gastroenterology (29.1%), gynaecology (29.1%) and thoracic medicine (22.4%). Among the included oncologists, the highest prevalences of prescription of neurotoxic anticancer drugs were platinum-based drugs (cisplatin (90.5%), carboplatin (82.4%) and oxaliplatin (70.0%)) and taxanes (paclitaxel (80.0%) and docetaxel (75.7%)) (Table 1).

Incidence and impact on patients' QoL

The incidence of CIPN (VAS score) was estimated at 36.2 ± 22.1% by the 210 oncologists (Table 2). A higher CIPN incidence was noted for gastroenterologists (43.9 ± 26.8%, $p = 0.005$, $n = 61$) than for other oncology specialties and a lower one for haematologists (24.5 ± 9.5%, $p < 0.001$, $n = 34$) (Table 2). A higher CIPN incidence was noted for oncologists prescribing oxaliplatin (38.2 ± 22.7%, $p = 0.03$, $n = 147$) than other prescribed anticancer drugs and lower incidences for vinorelbine (32.3 ± 19.0%, $p = 0.005$, $n = 129$), vinblastine (30.3 ± 17.5%, $p = 0.004$, $n = 64$), vincristine (29.5 ± 17.2%, $p < 0.001$, $n = 97$), vindesine (25.8 ± 14.9%, $p < 0.001$, $n = 33$), bortezomib (28.6 ± 14.0%, $p < 0.001$, $n = 50$) and thalidomide (27.8 ± 14.4%, $p < 0.001$, $n = 45$) (Table 3). The estimated CIPN incidence was not correlated with the number of chemotherapies prescribed per year (Spearman coefficient: − 0.07, $p = 0.34$).

The impact of CIPN on the QoL of patients (VAS score) was estimated at 57.1 ± 19.0 by oncologists (Table 2). Dermatologists estimated a higher impact of CIPN on the QoL of patients (67.7 ± 7.6, $p = 0.006$) and paediatricians (68.0 ± 5.0, $p = 0.03$) than other oncologists (Table 2). There was no difference of CIPN impact on the estimated QoL among prescribed anticancer drugs (Table 3). The score of CIPN impact was not correlated with the number of prescribed chemotherapies per year (Spearman coefficient: − 0.09, $p = 0.24$).

Table 1 Characteristics of the participants

Items	$N = 210$
Age (years)	45.3 ± 9.8
Women	107 (51.0%)
Profile	
Medical oncologist	195 (93.8%)
Surgical oncologist	5 (2.4%)
Radiotherapist	3 (1.4%)
General practitioner with oncologic orientation	2 (1.0%)
Unspecified	2 (1.0%)
Type of activities	
General hospital	92 (43.8%)
University hospital	56 (26.7%)
Private hospital	36 (17.1%)
Cancer centre	29 (13.8%)
Other	4 (1.9%)
Number of prescribed chemotherapies per year	500 [200; 1100]
Oncology specialties	
Gastroenterology	61 (29.0%)
Gynaecology	61 (29.0%)
Thoracic	48 (22.9%)
Haematology	34 (16.2%)
Oto-rhino-laryngology	31 (14.8%)
Urology	28 (13.3%)
Neurology	16 (7.6%)
General oncology	13 (6.2%)
Dermatology	7 (3.3%)
Maxillofacial	6 (2.9%)
Sarcoma	6 (2.9%)
Rheumatology/internal medicine	3 (1.4%)
Paediatric	3 (1.4%)
Radiotherapy	3 (1.4%)
Endocrinology	1 (0.5%)
Supportive care	1 (0.5%)
Unspecified	2 (1.0%)
Prescribed neurotoxic anticancer drugs	
Cisplatin	190 (90.5%)
Carboplatin	173 (82.4%)
Paclitaxel	168 (80.0%)
Docetaxel	159 (75.7%)
Oxaliplatin	147 (70.0%)
Vinorelbine	129 (61.4%)
Vincristine	97 (46.2%)
Eribulin	94 (44.8%)
Cabazitaxel	76 (36.2%)
Vinblastine	64 (30.5%)
Bortezomib	50 (23.8%)
Thalidomide	45 (21.4%)
Vindesine	33 (15.7%)
Vinflunine	16 (7.7%)
Other	9 (4.3%)

Quantitative results are presented by the mean and standard deviation, or by the median and [interquartile]. Qualitative results are presented by the number of answers and percentage

Prevention of CIPN

Among the participants, 97.1% (204/210) of oncologists evoked CIPN risk during the first consultation before starting

chemotherapy. In the case of CIPN risk factor, a therapeutic adjustment was reported by 68.4% (143/209) of oncologists, including a protocol change for 65.7% (94/143) or a dose reduction for 34.3% (49/143). Importantly, 31.6% (66/209) of oncologists reported that they made no therapeutic adjustment according to risk factors.

The use of drugs to prevent CIPN was reported by 9.6% (20/209) of oncologists. The main drugs used for the prevention of CIPN were group B vitamins (35.0%; 7/20), calcium and magnesium infusion (25.0%; 5/20) and pregabalin (15.0%; 3/20) (Fig. 2). Estimated incidences of CIPN were not different between oncologists who performed a therapeutic adjustment and those who did not (36.1 ± 22.0% vs. 36.6 ± 22.9%, $p = 0.88$) and between oncologists who used preventive drugs and those who did not (34.4 ± 20.5% vs. 36.5 ± 22.4%, $p = 0.67$).

Diagnostic of CIPN

During the medical follow-up, 99.5% (208/209) of oncologists declared that they assessed CIPN, 95.7% (200/209) did so systematically and 3.8% (8/209) on the patient's demand. Among them, 85.8% (175/204) of oncologists declared that they performed a clinical examination, 18.1% (37/204) asked for a neurological examination, 17.2% (35/204) used a questionnaire and 11.3% (23/204) held an interview with the patient. Clinical examinations were associated with questionnaires by 11.3% (23/204) of oncologists. The questionnaire the most frequently cited was the DN4 questionnaire for 50.0% (13/26) of them.

Management of CIPN

In the case of CIPN, a therapeutic adjustment of neurotoxic anticancer drugs was performed by 99.0% (207/209) of oncologists, among whom this therapeutic adjustment corresponded to a change of chemotherapy protocol (49.8%, 103/207), a dose reduction of neurotoxic anticancer drugs (30.9%, 64/207) or an interruption of neurotoxic anticancer drugs (19.3%, 40/207). About 47.3% (97/205) of oncologists considered that this therapeutic adjustment had a negative impact on patients' survival.

Among the participants, 72.9% (153/210) declared that they used drugs or therapeutic strategies to manage CIPN. Estimated incidences of CIPN were not different between oncologists using therapeutic strategies to manage CIPN and those who did not (35.7 ± 21.4% vs. 37.4 ± 24.3%, $p = 0.65$). Pregabalin (75.8%; 116/153) was mainly used, followed by amitriptyline (32.7%; 50/153) and gabapentin (25.5%; 39/153) (Fig. 3). Duloxetine was in only 4th position with 11.8% (18/153) of oncologists. It is noteworthy that 3 oncologists used calcium and magnesium infusion for CIPN management. Perceived efficacies (VAS scores) were different among the main drugs used (pregabalin, amitriptyline, gabapentin, duloxetine, oxycodone, capsaicin, B vitamins, tramadol, morphine) ($p = 0.003$), but not safety ($p = 0.11$). The efficacy of B vitamins was lower than for the other main drugs. Finally, advice from a pain physician could be demanded by 69.8% (143/205) of oncologists.

Discussion

The incidence of CIPN was estimated at about 36.2% by oncologists and tended to be lower than that described in the literature, which is close to 50% [4–6]. Digestive oncologists and those who prescribed oxaliplatin (reference drug for colorectal cancer) reported the highest incidence of CIPN (43.9% and 38.2%, respectively). Haematologists and those who prescribed vinca alkaloids (vinblastine, vincristine, vindesine and vinorelbine), thalidomide or bortezomib (reference drugs for haematological malignancies) reported the lowest incidence of CIPN (24.5%, 30.3%, 29.5%, 25.8%, 32.3%, 27.8% and 28.6%, respectively). There are no clear data in the

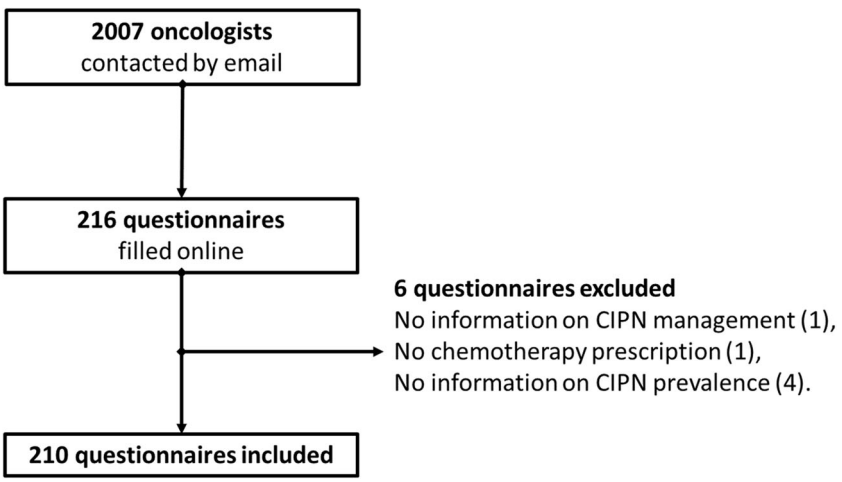


Fig. 1 Flowchart of questionnaire selection

Table 2 Estimated incidence of CIPN and impact on patient QoL according to oncology specialties

Oncology specialties	Incidence (%)	*p* values[#]	Effect size, 95% CI	Impact on QoL (%)	*p* values[#]	Effect size, 95% CI
Total ($N = 210$)	36.2 ± 22.1	–	–	57.1 ± 19.0	–	–
Dermatology ($n = 7$)	46.4 ± 23.2	0.28	0.48 [0.28; 1.23]	67.7 ± 7.6	0.006	0.58 [− 0.17; 1.33]
Endocrinology ($n = 1$)	30	–	–	65	–	–
Gastroenterology ($n = 61$)	43.9 ± 26.8	0.005	0.50 [0.20; 0.80]	55.8 ± 19.1	0.57	− 0.09 [− 0.39; 0.21]
General oncology ($n = 13$)	46.8 ± 19.7	0.06	0.51 [− 0.05; 1.07]	54.8 ± 20.7	0.69	− 0.13 [− 0.69; 0.43]
Gynaecology ($n = 61$)	36.0 ± 20.0	0.92	− 0.01 [− 0.31; 0.28]	59.2 ± 18.9	0.30	0.16 [− 0.14; 0.46]
Haematology ($n = 34$)	24.5 ± 9.5	< 0.001	− 0.64 [− 1.01; − 0.27]	52.7 ± 18.6	0.15	− 0.27 [− 0.64; 0.10]
Maxillofacial ($n = 6$)	39.0 ± 16.8	0.69	0.13 [0.68; 0.94]	62.2 ± 17.2	0.49	0.28 [0.53; 1.09]
Neurology ($n = 16$)	31.6 ± 15.1	0.24	− 0.22 [− 0.73; 0.28]	58.8 ± 17.8	0.70	0.10 [− 0.41; 0.60]
Oto-rhino-laryngology ($n = 31$)	36.4 ± 20.8	0.94	0.01 [− 0.37; 0.39]	54.1 ± 19.7	0.37	− 0.18 [− 0.56; 0.20]
Paediatric ($n = 3$)	26.7 ± 28.9	0.62	− 0.43 [− 1.57; 0.70]	68.0 ± 5.0	0.03	0.58 [− 0.55; 1.72]
Radiotherapy ($n = 3$)	36.7 ± 20.8	0.97	0.02 [− 1.11; 1.16]	66.0 ± 12.5	0.33	0.48 [− 0.66; 1.61]
Rheumatology/internal medicine ($n = 3$)	35.3 ± 30.2	0.97	− 0.04 [− 1.17; 1.10]	66.7 ± 19.1	0.47	0.51 [− 0.63; 1.65]
Sarcoma ($n = 6$)	38.3 ± 29.3	0.86	0.10 [− 0.71; 0.91]	55.8 ± 16.2	0.86	− 0.07 [− 0.87; 0.74]
Thoracic ($n = 48$)	32.9 ± 18.6	0.20	− 0.19 [− 0.51; 0.13]	57.7 ± 17.3	0.78	0.04 [− 0.28; 0.37]
Urology ($n = 28$)	42.4 ± 21.6	0.11	− 0.32 [− 0.08; 0.72]	57.5 ± 19.8	0.90	0.03 [− 0.38; 0.43]
Unknown ($n = 30$)	30.5 ± 15.4	0.048	− 0.30 [− 0.69; 0.09]	58.0 ± 18.9	0.77	0.06 [− 0.33; 0.44]

Results are presented by the mean and standard deviation

[#] Versus other specialties

literature regarding which anticancer drugs are the most neurotoxic. Based on the study of Shah et al., patients receiving bortezomib had the highest prevalence of CIPN (88%), followed by oxaliplatin (79%), thalidomide (67%), paclitaxel (65%) and vincristine (61%) [6]. The review and meta-analysis of Seretny et al. presented the following incidences: bortezomib and thalidomide (96.2%), oxaliplatin (40.6–93.7%), paclitaxel (59.2–92.8%), cisplatin (12.1–85.7%), cisplatin and paclitaxel (69.2–76%), bortezomib (46.7%), thalidomide (32.1–96%), cisplatin and vincristine (20.1%), and vincristine (19.6%) [4]. The recent study by Gewandter et al., based on US health plan claims and administrative data, reported a CIPN incidence of 3.6–18.1% within 6 months of the initiation of chemotherapy. Authors suggested that as used currently by clinicians, administrative codes likely underestimate CIPN incidence [24]. Our results therefore seem to be in accordance with those in the literature showing an underestimation of the incidence of CIPN by oncologists [14, 24].

The great majority of oncologists evoked the risk of CIPN with their patients before starting the chemotherapy protocol, and two-thirds of them proposed a therapeutic adjustment in the case of neuropathy risk factors. A minority of oncologists (9.5%) declared that they used preventive strategies, including group B vitamins, calcium/magnesium and pregabalin. This is consistent with the literature, because to date, no effective preventive strategy can be recommended [10, 11]. In a randomized, placebo-controlled trial, group B vitamins were not effective in preventing CIPN [25]. Calcium/magnesium infusions for the prevention of oxaliplatin-induced peripheral neuropathy have been debated for a long time and should not be recommended for the prevention of CIPN [26]. Regarding pregabalin, a double-blind randomized controlled trial demonstrated its ineffectiveness in preventing the development of oxaliplatin-induced peripheral neuropathy [27]. The same observation was made for paclitaxel-induced peripheral neuropathy [28].

Nearly all the oncologists declared that they assessed CIPN during the medical follow-up of patients, and 63% of them performed a clinical examination. Some oncologists mentioned the use of the DN4 questionnaire which helps in the screening of neuropathic pain [29]. Neuropathic pain is probably one of the most debilitating symptoms, but pain affects only 20–30% of patients with CIPN [30]. Caution is necessary when using the DN4 questionnaire, because it could lead to an underestimation of CIPN symptoms, excluding patients with non-painful symptoms such as tingling or numbness [30]. CIPN assessment is also dependent on the type of neurotoxic anticancer drugs used, meaning that each assessment tool should be specific to neurotoxic anticancer drugs [31]. The clinical assessment of CIPN is still a concern in clinical practice [4]. There is no guideline for the diagnosis of CIPN in routine activity, but several recommendations have been proposed with the association of patient-reported outcomes (PROs) and clinician-reported outcomes (CROs) [32]. The ACTTION (Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks) recommendations encourage the systematic use of PROs for clinical trials assessing preventive strategies for

Table 3 Estimated incidence of CIPN and impact on patient QoL according to the anticancer drugs prescribed

Anticancer drugs prescribed	Incidence (%)	*p* values[#]	Effect size, 95% CI	Impact on QoL (%)	*p* values[#]	Effect size, 95% CI
Total ($N = 210$)	36.2 ± 22.1	–	–	57.0 ± 18.9	–	–
Bortezomib ($n = 50$)	28.6 ± 14.0	< 0.001	− 0.45 [− 0.77; − 0.13]	54.3 ± 19.0	0.25	− 0.19 [− 0.51; 0.13]
Cabazitaxel ($n = 76$)	35.9 ± 20.3	0.93	− 0.01 [− 0.29; 0.27]	56.4 ± 19.7	0.71	− 0.05 [− 0.34; 0.23]
Carboplatin ($n = 173$)	35.3 ± 21.1	0.29	− 0.22 [− 0.58; 0.13]	55.9 ± 18.6	0.09	− 0.33 [− 0.69; 0.02]
Cisplatin ($n = 190$)	36.5 ± 21.9	0.48	0.18 [− 0.28; 0.64]	57.4 ± 19.1	0.43	0.17 [− 0.29; 0.63]
Docetaxel ($n = 159$)	37.0 ± 21.3	0.37	0.16 [− 0.16; 0.47]	58.1 ± 19.0	0.15	0.23 [− 0.08; 0.55]
Eribulin ($n = 94$)	34.9 ± 18.7	0.46	− 0.10 [− 0.37; 0.17]	57.0 ± 18.9	0.99	− 0.002 [− 0.28; 0.27]
Oxaliplatin ($n = 147$)	38.2 ± 22.7	0.03	0.31 [0.02; 0.61]	55.9 ± 19.0	0.18	− 0.20 [− 0.50; 0.09]
Paclitaxel ($n = 168$)	37.0 ± 21.5	0.34	0.18 [− 0.16; 0.52]	57.7 ± 19.0	0.36	0.16 [− 0.18; 0.50]
Thalidomide ($n = 45$)	27.8 ± 14.4	< 0.001	− 0.49 [− 0.82; − 0.15]	55.4 ± 19.0	0.53	− 0.11 [− 0.44; 0.23]
Vinblastine ($n = 64$)	30.3 ± 17.5	0.004	− 0.39 [− 0.68; − 0.09]	55.2 ± 18.1	0.34	− 0.14 [− 0.43; 0.15]
Vincristine ($n = 97$)	29.5 ± 17.2	< 0.001	− 0.57 [− 0.85; − 0.30]	57.2 ± 19.0	0.94	0.01 [− 0.26; 0.28]
Vindesine ($n = 33$)	25.8 ± 14.9	< 0.001	− 0.56 [− 0.94; − 0.19]	55.4 ± 17.9	0.58	− 0.10 [− 0.47; 0.27]
Vinflumine ($n = 16$)	31.7 ± 21.8	0.41	− 0.21 [− 0.72; 0.29]	51.6 ± 21.6	0.30	− 0.31 [− 0.82; 0.20]
Vinorelbine ($n = 129$)	32.3 ± 19.0	0.003	− 0.46 [− 0.74; − 0.18]	56.6 ± 18.9	0.64	− 0.07 [− 0.34; 0.21]
Other ($n = 9$)	37.9 ± 14.5	0.73	0.08 [0.59; 0.75]	47.7 ± 14.7	0.08	− 0.52 [− 1.18; 0.15]

Results are presented by the mean and standard deviation

[#] Versus other anticancer drugs

CIPN. Measures of clinician-rated neuropathy signs (e.g. vibration and pinprick sensation) and function measures (e.g. balance) are also encouraged [33]. There is significant evidence that the prevalence of CIPN is greater with PROs than with CROs [34] and PROs identify functional impairment earlier than CROs [35, 36]. However, we must admit that the systematic screening of CIPN with PROs and CROs may represent a supplementary workload, which is already high for oncologists [37].

About 72.9% of oncologists declared that they use drugs to manage CIPN and the main drug used was pregabalin, although this treatment is not recommended [10, 11]. Indeed, 3 double-blind randomized placebo-controlled trials have assessed the efficacy of pregabalin in treating CIPN and failed to demonstrate any curative effect [27, 28, 38]. Conversely, only 11.2% of oncologists declared that they use duloxetine, which is the reference drug according to ASCO recommendations [10, 11]. It is also of note that 27 oncologists mentioned the use of opioids for the management of CIPN, although their efficacy remains limited for its treatment [39].

Very few studies have been performed on clinical practices specific to CIPN. To our knowledge, two Japanese studies assessed the management practices of CIPN, before and after the publication of the Japanese guidelines relating to CIPN management (CIPN-GL2017). Duloxetine is the only drug recommended for the management of CIPN in Japanese patients [40, 41], in line with the ASCO guideline [11]. The most frequently administered drugs for the treatment of numbness, before and after the guideline's publication, were antiepileptic drugs that included pregabalin (68.3% and 65.4%, $p = 0.48$), vitamin B_{12} (42.7% and 38.3%, $p = 0.31$), Kampo compounds such as goshajinkigan, a traditional Japanese medicine (24.1% and 22.0%, $p = 0.62$), and duloxetine (21.0% and 39.0%, $p < 0.01$). Regarding pain, before and after the guideline's publication, the most frequently prescribed drugs were non-

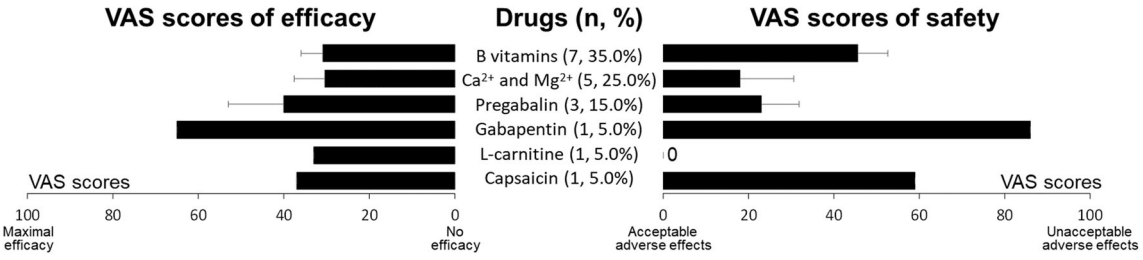
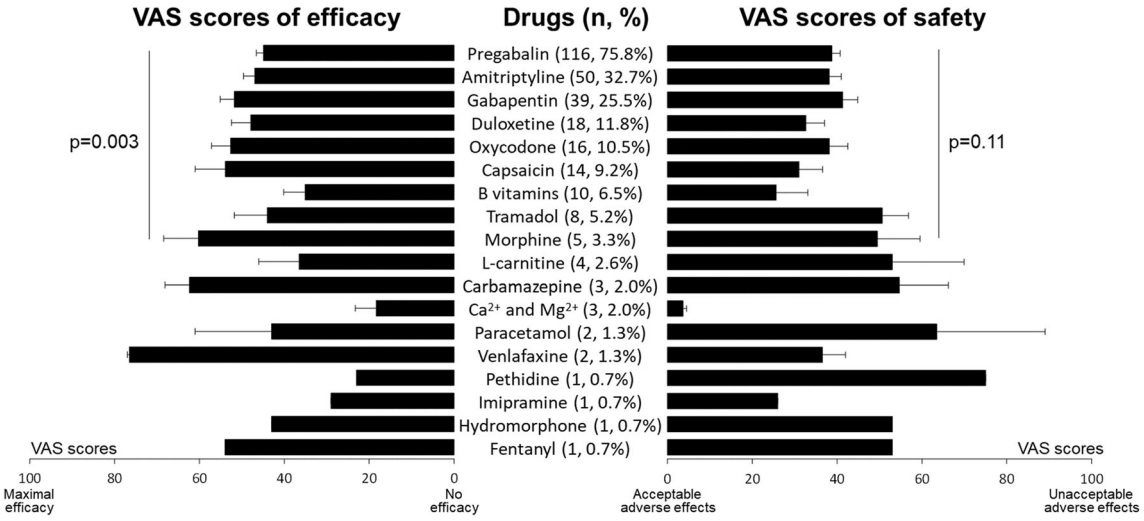


Fig. 2 Drugs used to prevent CIPN, perceived efficacy and safety. For each drug, the results are presented with the number of oncologists using it among the 20 oncologists using medications. The VAS scores of the perceived efficacy and the perceived safety. The results are presented by the mean and the standard error of the mean



Comparison of efficacy between drugs (p-values)

Pregabalin	**Pregabalin**								
Amitripyline	p=0.62	**Amitriptyline**							
Gabapentin	p=1.00	p=0.86	**Gabapentin**						
Duloxetine	p=0.98	p=0.74	p=1.00	**Duloxetine**					
Oxycodone	p=0.31	p=0.22	p=0.65	p=0.98	**Oxycodone**				
Capsaicin	p=0.17	p=0.06	p=0.32	p=0.75	p=0.99	**Capsaicin**			
B vitamins	**P<0.001**	**p<0.001**	**p=0.004**	**p=0.003**	**p<0.001**	**p<0.001**	**B vitamins**		
Tramadol	p=0.70	p=0.33	p=0.93	p=0.87	p=0.28	p=0.23	**p=0.049**	**Tramadol**	
Morphine	p=0.97	p=0.71	p=1.00	p=1.00	p=1.00	p=0.98	**p=0.03**	p=0.84	**Morphine**

Fig. 3 Drugs used to manage CIPN, perceived efficacy and safety. For each drug, the VAS scores of the perceived efficacy and the perceived safety are presented with the number of oncologists using it among the 153 oncologists using medications. Results are presented by the mean and the standard error of the mean. Comparisons of perceived efficacies and safeties have been performed for the main drugs used (amitriptyline, gabapentin, duloxetine, oxycodone, capsaicin, B vitamins, tramadol and morphine). Perceived efficacies among the main drugs were significantly different ($p = 0.003$), and perceived safeties were not different ($p = 0.11$). Table presents the post hoc p values for the two-by-two comparisons of the perceived efficacies between drugs

steroidal anti-inflammatory drugs (71.7% and 43.2%, $p < 0.01$), opioids (40.9% and 35.1%, $p = 0.18$), antiepileptic drugs (42.6% and 46.9%, $p = 0.32$) and duloxetine (11.1% and 43.0%, $p < 0.01$) [40, 41]. It is noteworthy that the authors suggested that the publication of the CIPN-GL2017 guideline may have influenced the administration preferences of oncologists and increased duloxetine use [41]. These two studies underline that duloxetine is used less than pregabalin by Japanese oncologists, which is also the case in France, and that duloxetine is used less by French oncologists than Japanese ones. Finally, three studies assessed nursing practices and knowledge. The main results of these studies were the lack of knowledge relating to CIPN and assessment tools [42–44].

In addition to pharmacological treatments for CIPN, there is a growing number of studies evaluating non-pharmacological approaches to prevent or manage CIPN. Among these approaches, cryotherapy (frozen gloves ± socks) has yielded interesting but limited results on CIPN symptoms [45–47] and has raised concerns about tolerability [46]. Physical activity appears to be a safe and effective strategy to reduce symptoms in patients with CIPN [48–50].

The main limitation of this study was the small number of participants, who represent only 12.5% of the oncologists contacted. Consequently, outcomes with small numbers of answers must be interpreted with caution. Selection bias should be limited since nearly all the French regions and oncology specialties were represented in the study. Moreover, the sample of oncologists included in the study was quite representative of French oncologists (data from the French National Cancer Institute in 2016: medical oncologists: 1009, mean age: 47-year, and women: 52%) [51]. A cognitive bias is certainly present, since the main variables are subjective (VAS). Oncologists prescribed several different anticancer drugs, even different neurotoxic ones, which may represent a confounding factor. Consequently, it was not possible to specifically assess the estimated CIPN incidence for specific types of cancer. However, one of the objectives was to capture the perception of oncologists regarding CIPN incidence, and the results obtained are not aberrant when viewed in the light of the literature.

Conclusion

French oncologists have a tendency to underestimate the incidence of CIPN, and this perception appears to be dependent on oncology specialties. CIPN management strategies

appeared suboptimal regarding current recommendations (majority use of pregabalin and minority use of duloxetine). The method of transmission of ASCO recommendations for the management of CIPN [10, 11] must be reviewed in order to improve their dissemination to French oncologists and enable the latter to integrate them in their daily clinical practice.

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Data availability Upon request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

Ethics approval The study was approved by an ethics committee (No.2019/CE08, 18/02/2019, IRB: 00008526).

Consent to participate Consent was obtained by the answer to the survey.

Consent for publication Not applicable.

Code availability Not applicable.

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