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PREVALENCE AND PREDICTORS OF CHEMO THERAPY INDUCED PERIPHERAL NEUROPATHY IN CANCER PATIENTS: A SYSTEMATIC REVIEW STUDY

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Abstract:

Background: *Chemotherapy-induced peripheral neuropathy (CIPN) is a disabling pain condition resulting from chemo-therapy treatment for cancer. Severe acute CIPN may require chemotherapy dose reduction or cessation. There is no effective CIPN prevention strategy; treatment of established chronic CIPN is limited, and the prevalence of CIPN is not known.*

Method*: Embase, Medline, CAB Abstracts, CINAHL, PubMed central, Cochrane Library, and Web of Knowledge for relevant references were used and used random-effects meta-regression to estimate overall prevalence. We assessed study quality using the CONSORT and STROBE guidelines, and we report findings according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance.*

Results: *We provide a qualitative summary of factors reported to alter the risk of CIPN.31 studies with 4179 patients were used in the study. Data from CIPN prevalence was 68.1% (57.7–78.4) when measured in the first month after chemotherapy, 60.0% (36.4–81.6) at 3 months and 30.0% (6.4–53.5) at 6 months or more. Different chemotherapy drugs were associated with differences in CIPN prevalence. Genetic risk factors were reported in 4 studies. Clinical risk factors, identified in 4 of 31 studies, included neuropathy at baseline, smoking, abnormal creatinine clearance, and specific sensory changes during chemotherapy.*

Conclusion*: CIPN prevalence decreases with time, at 6 months 30% of patients continue to suffer from CIPN. Routine CIPN surveillance during post-chemotherapy follow-up is needed. A number of genetic and clinical risk factors were identified that require further study.*

Key words: *Chemotherapy-induced peripheral neuropathy (CIPN), Prevalence, Risk factors.*

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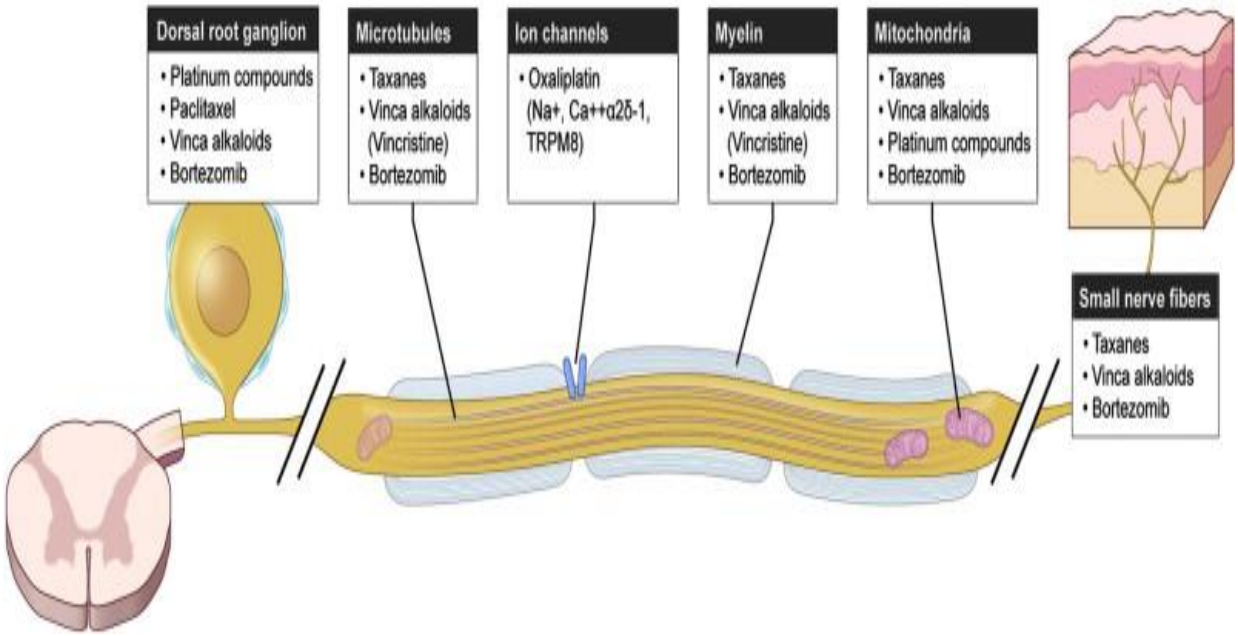

Fig 1: chemotherapy Agents effects on sensory changes

INTRODUCTION:

Advancement in better cancer therapies, including targeted chemotherapeutic agents, come longer patient survival times and the potential for long-term treatment-related side effects. Chemotherapy-induced peripheral neuropathy (CIPN) might have a severe side effect often associated with several chemotherapeutic agents including the platinum agents, taxanes, vinca alkaloids, thalidomide, and bortezomib fig 1.CIPN is mostly dose dependent and progressive while receiving and after such treatment [1-3]. In severe neuropathy pain cases, CIPN can lead to dose reductions, changes in chemotherapy protocols, or termination of a therapeutic agent the pain, is associated with sensory changes, and weakness.

The morbidity associated with CIPN can lead to pronounced alterations in quality of life and independent performance of activities of daily living [4,5]. The etiology, specific pathogenesis and pathophysiological effects of specific agents are not clearly understood [4,6]. A meta-analysis of more than 4000 chemotherapy-treated patients found the prevalence of CIPN to be 68.1% within the first month of chemotherapy treatment, 60.0% at 3 months, and 30.0% at 6 months [6]. Treatments to prevent CIPN are inadequate. Meta-analyses of clinical trials for CIPN prevention report inconclusive results [7,8] Treatment options for established CIPN are also limited. Clinical trials of antiepileptic or anti-depressant agents to treat other neuropathic pain conditions have generally been negative [9]. Only 1 recent, double-blind, randomized controlled trial showed improvement in CIPN symptoms after 5 weeks of treatment with duloxetine.

Previous studies of CIPN have combined narrative review with expert opinion, with potential risk of bias. The aim of this systematic review is to find the incidence and prevalence and risk factors of CIPN.

METHOD:

Search strategy:

Embase, Medline, CAB Abstracts, CINAHL,PubMed central, Cochrane Library and Web of Knowledge data bases were used. Searches were not limited by date restrictions. Search terms were free text and included; [‘‘Chemotherapy Induced Peripheral Neuropathy’’ OR ‘‘Chemo-therapy Induced Neurotoxicity’’ OR ‘‘Chemotherapy Induced Neurotoxicity Syndromes’’ OR ‘‘CIPN’’ AND [‘‘Predictors’’ OR ‘‘Risk Factors’’]. The search strategy was adapted for each database.

Inclusion and exclusion criteria:

Prospective observational studies of adult cancer patients receiving chemotherapy of any type were included in this study. Our definition of observational studies included cohort studies in which patients were prospectively identified and followed up using relevant pre-defined outcomes of interests. We also included control group data from randomized controlled trials (RCTs) of CIPN prevention in which

details of the patients who developed CIPN were reported. Studies were excluded if they described animal models of CIPN, were investigating CIPN treatment or prevention, included pediatric populations, or investigated other causes of neuropathy in cancer patients (eg, pre-existing neuropathy such as diabetic neuropathy or other cancer related causes of neuropathy such as post-mastectomy). Fig 2.

CIPN Incidence and Prevalence Systematic Review and Meta-Analysis PRISMA 2009 Flow Diagram

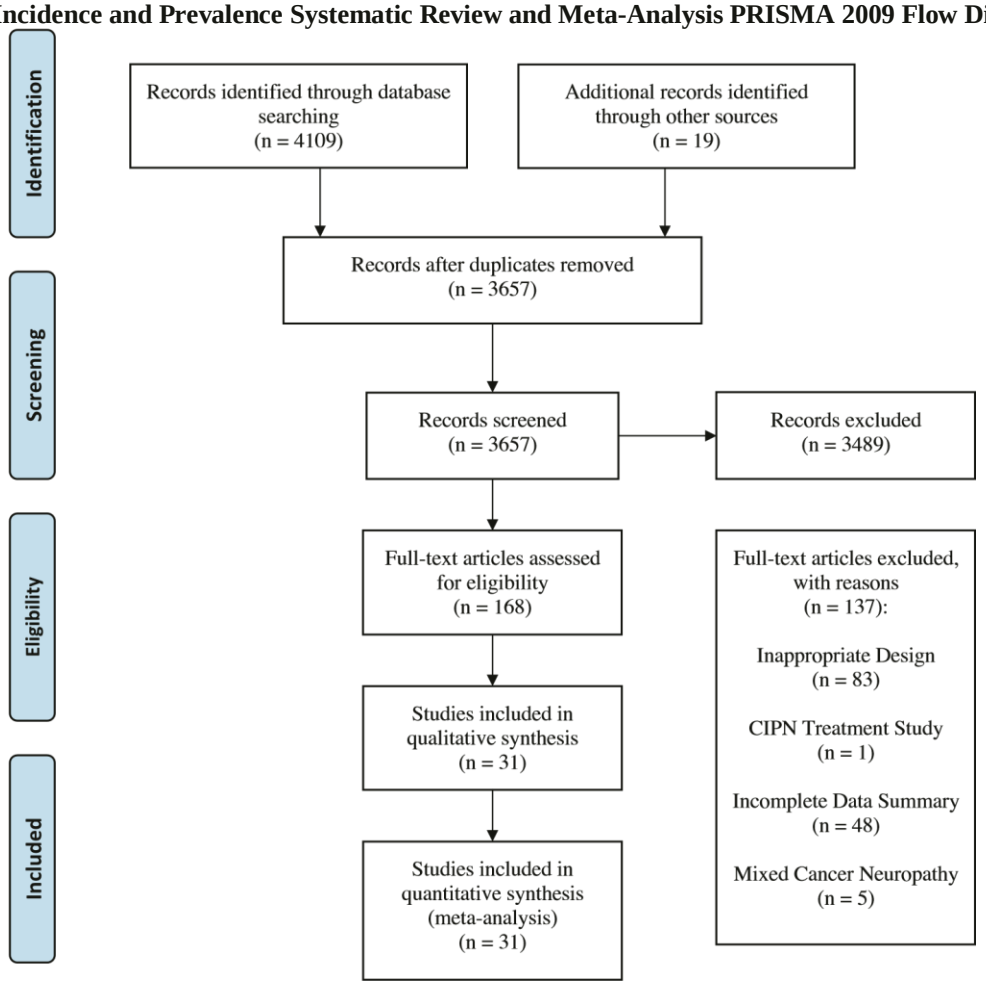

Fig. 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 flow diagram.

Data synthesis and analysis:

Our primary outcome was the prevalence of CIPN. Random effects meta-regression to quantify heterogeneity and its potential sources were used. Therefore, we included chemotherapy type, last time point of CIPN assessment, and measures of study quality as independent variables in our regression model. We also planned for assessment of risk factors for CIPN across studies. We appraised studies using STROBE criteria for observational studies and CONSORT criteria for trials. In open label studies (Table 1), we modified the CONSORT criteria by not considering the point for blinding, to account for the design of these studies. STATA 13.1 was used for statistical analyses.

Table 1: Overview of included studies.

First author (year)	Study type and quality (CONSORT/STROBE score)	Incidence (95% CI)	Main cancer class (chemotherapy)	Dose (mg/m^2) (mean or cumulative)
Antonacopoulou (2009)*	Prospective cohort	58.8% (42.2–75.3)	Colorectal (oxaliplatin)	—
Argyriou (2006)	Prospective cohort (18/22)	61.5% (35.1–87.9)	Breast (paclitaxel)	1980
		42.8% (16.9–68.7)	Lung (cisplatin)	720
Argyriou (2007) [8]	Prospective cohort (19/22)	64% (45.2–82.8)	Colorectal (oxaliplatin)	1740
Argyriou (2007)	Prospective cohort (19/22)	69.2% (44.1–94.3)	Multiple solid (cisplatin and paclitaxel)	1267
Argyriou (2012)	Prospective cohort (19/22)	83.3% (77.3–89.3)	Colorectal (oxaliplatin)	1646
Argyriou (2013)	Prospective cohort (20/22)	84.5% (79.4–89.5)	Colorectal (oxaliplatin)	1651
Attal (2009)	Prospective cohort (19/22)	66.6% (44.8–88.4)	Colorectal (oxaliplatin)	1278
Baldwin (2012)	Prospective cohort (20/22)	67.2% (64.1–70.3)	Breast (paclitaxel)	—
Cascinu (1995)	RCT (18/25)	64% (45.2–82.8)	Gastrointestinal (cisplatin)	—
Cascinu (2002)	RCT (16/25)	78.9% (60.6–97.3)	Colorectal (oxaliplatin)	783
Chaudhary (2008)	Prospective cohort (13/22)	96.2% (89.2–103)	Multiple myeloma (bortezomib and thalidomide)	36
Dimopoulos (2011)	RCT (21/25)	46.7% (41.4–52.1)	Multiple myeloma (bortezomib)	384
Gandara (1995)	RCT (18/25)	12.1% (5.6–185)	Ovarian and lung (cisplatin)	379
Ghoreishi (2012)	RCT (19/25)	59.2% (40.7–77.8)	Breast (paclitaxel)	—
Glendenning (2010)	Cross sectional cohort (21/22)	20.1% (15.5–24.7)	Testicular (cisplatin and vincristine)	400
Gobran (2013)	RCT (13/25)	70% (53.6–86.4)	Colorectal (oxaliplatin)	763
Ishibashi (2010)	RCT (20/25)	93.7% (81.9–105)	Colorectal (oxaliplatin)	728
Johnson (2011)	RCT (23/25)	32.1% (29.1–34.9)	Multiple myeloma (thalidomide)	—
		19.6% (16.3–22.9)	(Vincristine)	—
Kawakami (2012)	Prospective cohort (14/22)	76% (64.1–87.8)	Lung (cisplatin and paclitaxel)	—
Kemp (1996)	RCT (19/25)	675% (59.2–75.8)	Gynecological (cisplatin)	—
Krishnan (2005)	Prospective cohort (16/22)	50% (25.5–74.5)	Colorectal (oxaliplatin)	1200
Lin (2006)	Randomised trial (15/24)	90% (71.4–108)	Colorectal (oxaliplatin)	1200
Milla (2009)	Randomised trial (11/24)	92.8% (79.3–106)	Colorectal (oxaliplatin)	772

Pace (2003)	Randomised trial (11/24)	85.7% (67.4–104)	Multiple solid (cisplatin)	420
Pace (2007)	Prospective cohort (14/22)	92.8% (79.4–106)	Breast (paclitaxel)	1744
Pace (2010)	RCT (19/25)	41.6% (21.9–61.4)	Multiple solid (cisplatin)	450
Planting (1999)	Randomised trial (13/24)	13.5% (2.5–24.5)	Multiple solid (cisplatin)	401
Plasmati (2002)	Prospective cohort (15/22)	96% (88.3–103)	Multiple myeloma (thalidomide)	18
Van der Hoop (1999)	RCT (12/25)	41.6% (13.7–69.5)	Gynecological (cisplatin)	416
Von Schlippe (2001)	Prospective cohort (9/22)	17.2% (3.4–30.9)	Testicular (cisplatin)	—
Won (2012)	Prospective cohort (16/22)	40.6% (30.8–50.4)	Colorectal (oxaliplatin)	935

Abbreviation: RCT, randomized controlled trial (note that randomized trials, as opposed to RCTs, did not have blinding or placebo). — Cumulative or average dose not reported. Reported cumulative dose refers to actual dose received.*Abstract only available; STROBE assessment not possible. Where upper 95% confidence intervals exceeded 100, only 100% were recorded, as this is clinically interpretable. Study pooled incidence across chemotherapy types included.àStudy pooled incidence across cancer types.

RESULTS AND DISCUSSION:

4128 potentially relevant studies, and examined the full text of 138. A total of 31 studies (involving 4179patients) met our inclusion criteria. A total of 30 studies reported the incidence of CIPN (new CIPN cases divided by the population at risk). One study reported CIPN prevalence (all CIPN cases divided by population at risk) Because CIPN might have occurred, and resolved, between study assessments, we calculated the prevalence of CIPN at the time of each assessment.

CIPN incidence and prevalence:

1960 developed CIPN (aggregate prevalence48%) out of 4179 patients. CIPN prevalence was 68.1% (95% CI = 57.7–78.4) within the first month of the end of chemotherapy, 60.0% (36.4–81.6) at 3 months, and 30.0% (6.4–53.5) at 6 months or later (Table 2). An overview of the individual incidence reported in included studies is shown in Table 1.

Cumulative dose (CD) of chemotherapy (actual dose received) in our meta-regression was not included in the study because standard and maximally tolerated doses would differ substantially from drug to drug (study-specific cd shown in Table 1). As its predicted that, there was co-linearity between the cancer type and the chemotherapy used; because we reasoned that it is more likely that CIPN prevalence would be related to drug than to cancer type, we considered only chemotherapy type in our regression model (Table 3). The type of chemotherapy used accounted for 32% of the observed heterogeneity in our sample (adjusted R2= 0.315, P< .04).

Table 2: Comparison of prevalence related to time of CIPN assessment.

Time of assessment (after cessation of chemotherapy)	Prevalence (95% CI)	Studies included	Total no. of patients in group
61 mo	68.1% (57.7–78.4)	Antonacopolou 2009 Argyriou 2007 Argyriou 2012 Argyriou 2013 Baldwin 2012 Cascinu 1995 Cascinu 2002 Chaudhry 2008 Dimopoulos 2011* Gandara 1995 Ghoreishi 2012 Gobran 2013* Ishibashi 2010 Kawakami 2012 Krishnan 2005* Lin 2006 Milla 2009* Pace 2003 Pace 2007* Pace 2010 Van Der Hoop 1999 Won 2012	2085
3 mo	60.0% (36.4–81.6)	Argyriou 2006 Argyriou 2007 Kemp 1996 Planting 1999 Plasmati 2007	234
P6 mo	30.0% (6.4–53.5)	Johnson 2011 Attal 2009 Glendenning 2010 Von Schlippe 2001	1860

Abbreviations: CI, confidence interval; CIPN, chemotherapy-induced peripheral neuropathy.*Studies included longer-term CIPN follow up but did not provide enough details at these later time points to allow use of data in the meta-regression. Wide confidence interval likely due to small number of studies assessing CIPN beyond this time point.àStudy considered CIPN only after induction therapy and not during maintenance.

Table 3 Studies stratified by drug type

	Study type (CONSORT/STROBE	Main cancer class	CIPNseverity report (count by grade if given)	CIPNassessment time points	CIPNassessment method(s)
Antonacopoulou (2009)*	Prospective cohort	Colorectal	NR	Unclear	TNSc
Argyriou (2007) [8]	Prospective cohort	Colorectal	Grade I (6/16)	Baseline	TNSc
			Grade II (8/16)	Cycles 4, 8, 12	NPS
			Grade III (2/16)		NCI-CTC
Argyriou (2012)	Prospective cohort	Colorectal	Grade I (38/125)	Baseline	TNSc
			Grade II (46/125)	Cycles 3, 6 (FOLFOX)	NPS
			Grade III (41/125)	Cycles 4, 8 (XELOX)	NCI-CTC
Argyriou (2013)	Prospective cohort	Colorectal	Grade I (62/169)	Baseline	TNSc
			Grade II (46/169)	Cycle 6, 12 (FOLFOX)	NCI-CTC
			Grade III (61/169)	Cycles 4, 8 (XELOX)	
Attal (2009)	Prospective cohort	Colorectal	Sensory symptom counts described as means/ individual	Baseline Cycle 3, 6, 9 12 ± 2 mo after chemo end	NCI-CTC NPS (EORTC) QLQ-C30
Cascinu (2002)	RCT	Colorectal	Grade I (4/15)	Baseline	NCI-CTC
			Grade II (6/15)	Cycles 4, 8, 12	NPS
			Grade III (4/15)	Within 2 wk of chemo end	
			Grade IV (1/15)		
Gobran (2013)	RCT	Colorectal	Grade I (7/21)	Unclear if at baseline	NCI-CTC
			Grade II (0/21)	At each chemo cycle until end of chemo (variable no. of cycles)	
			Grade III (14/21)	Longer follow-up for those with CIPN (but denominator unclear)	
			Grade IV (0/21)		
Ishibashi (2010)	RCT	Colorectal	Grade I (15/15)	Baseline	NCI-CTC
			Grade II (1/15)	At each chemo cycle until end of chemo	
			Grade III (0/15)		
			Grade IV (0/15)		
Krishnan (2005)	Prospective cohort	Colorectal	NR	No baseline	NCI-CTC
				Within 1 mo of chemo end only reported assessment	NPS TNSc
Lin (2006)	Controlled trial	Colorectal	Grade I (1/9)	Baseline	NCI-CTC
			Grade II (5/9)	Cycles 4, 8, 12	NPS
			Grade III (3/9)	Within 2 wk of end of chemo	
			Grade IV (0 / 9)		
Milla (2009)	Controlled trial	Colorectal	Grade I (0/13)	Baseline	NCI-CTC
			Grade II (9/13)	Cycles 5, 9, 12	NES
			Grade III (4/13)	(Some followed up longer but denominator unclear)	
Won (2012)	Prospective cohort	Colorectal	NR	Unclear if at baseline	NCI-CTC
				At each chemo cycle until end of chemo (variable no. of cycles)	NES
Cisplatin: 42.2% (95% CI = 21.3–63.1)					

Argyriou (2006)	Prospective cohort	Lung	Reported by age group only	Baseline Cycles 3, 6 3 mo after chemo end	PNS NPS
Cascinu (1995)	RCT	Gastrointestinal	Grade I (3/16) Grade II (10/16) Grade III (2/16) Grade IV (1/16)	Baseline After 9 and 15 wk of therapy Within 1 wk after end of chemo	NCI-CTC NPS
Gandara (1995)	RCT	Ovarian and lung	Only grade P3 reported	Unclear if at baseline At each cycle until chemo end (variable no. of cycles) Study stopped early after interim analysis due to high toxicity in intervention group	NCI-CTC
Kemp (1996)	RCT	Gynecological	Grade I (31/81) Grade II (35/81) Grade III (15/81)	Baseline Cycles 4, 5, 6 Monthly after chemo for 3 mo	NCI-CTC NES
Pace (2003)	Controlled trial	Multiple solid	Grade I (6/12) Grade II (4/12) Grade III & IV (2/12)	Baseline After 6 cycles	TNSc NES
Pace (2010)	RCT	Multiple solid	Only grade P3 reported	Baseline Every cycle for 3 cycles 1 mo after chemo end	TNSc NPS
Planting (1999)	Controlled trial	Multiple solid	Grade I (5/5)	Baseline Cycle 3, 6 3 mo after chemo end (Longer follow-up but no denominator info)	NCI-CTC NES
Van der Hoop (1999)	Controlled trial	Gynecological	Mean vibration threshold	Baseline Cycles 2, 4, 6 End of chemo	NES

CIPN risk factors:

Eight of the included studies assessed risk factors for CIPN(Table 4).Four genome-wide association studies (GWAS), totaling 2671 patients, sought single nucleotide polymorphisms (SNPs) associated with CIPN. All GWAS used validation datasets and conducted genotyping blinded to clinical status. These reported polymorphisms associated with arrange of proteins, including voltage-gated sodium channels, Schwann cell function–related proteins, and receptors for cell surface collagen, receptors involved in neuronal apoptosis, neuronal crest cell development, and an enzyme involved in pyruvate metabolism.

reported clinical risk factors for CIPN included baseline neuropathy, a history of smoking, decreased creatinine clearance, and specific sensory changes during chemotherapy treatment, including cold allodynia (pain in response to a non-painful cold stimulus) and cold hyperalgesia (exaggerated pain in response to a painful cold stimulus, 20°C).

CONCLUSION:

CIPN prevalence decreases with time, at 6 months 30% of patients continue to suffer from CIPN. Routine CIPN surveillance during post-chemotherapy follow-up is needed. A number of genetic and clinical risk factors were identified that require further study.

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