

Supportive Care Update: Chemotherapy Induced Nausea and Vomiting, Mucositis and Neuropathy

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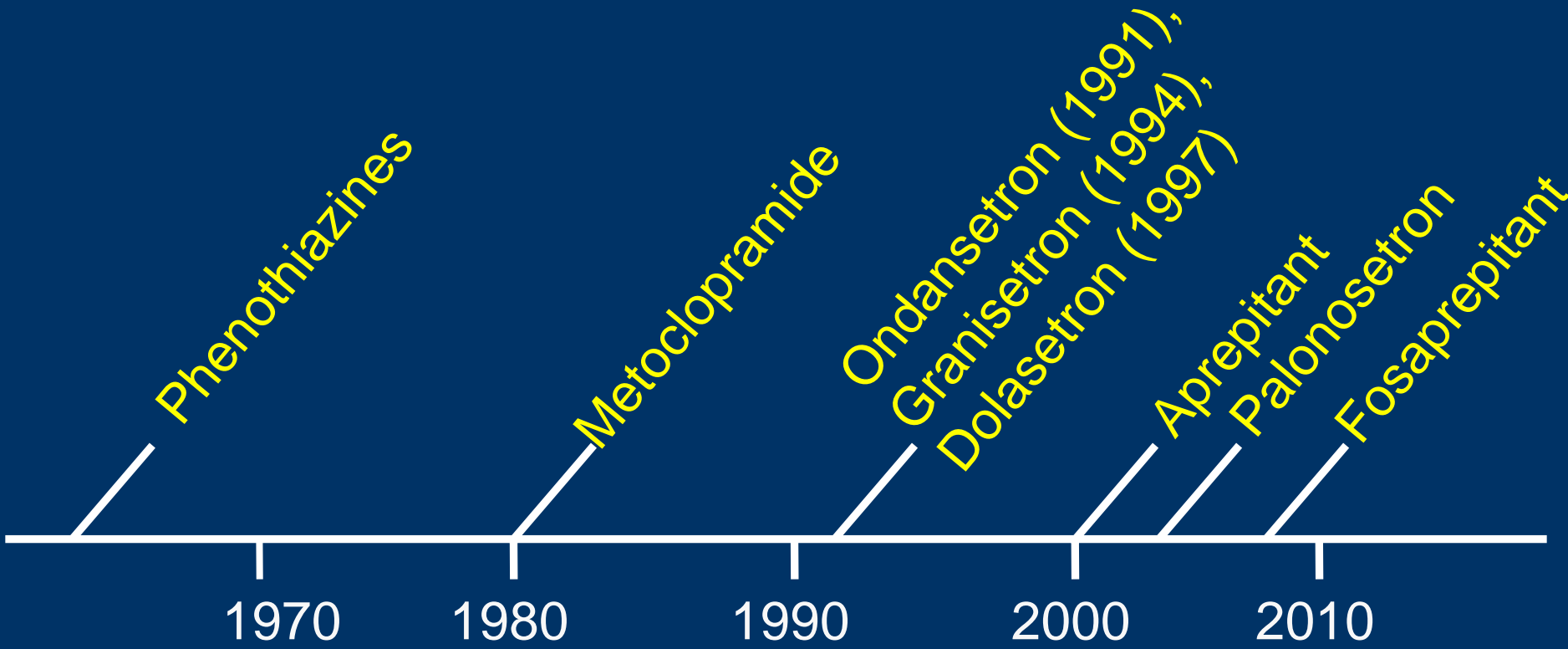
Objectives

- To provide an update on the pharmacotherapy and new agents available for the management of the following **chemotherapy-induced** conditions:
 - Nausea and Vomiting
 - Oral Mucositis
 - Peripheral Neuropathy

Chemotherapy Induced Nausea and Vomiting (CINV)



Antiemetics Timeline



Patients' Perceptions of CINV

1983 Vomiting # 1 side effect

1993 Vomiting # 5 side effect
Nausea # 1 side effect

2006 Nausea >>> Vomiting affecting QOL

Antiemesis Guidelines: ASCO

Chemo Emetogenicity	Acute (Day 1)	Delayed (Days 2 onwards)
High (90% & above)	5-HT ₃ antagonist + dexamethasone + NK1 antagonist	Dexamethasone + NK1 antagonist
Moderate (30% - 90%)	5-HT ₃ antagonist + dexamethasone	Dexamethasone OR 5-HT ₃ antagonist
Low (10 %- 30%)	Dexamethasone or others	None
Minimal (<10%)	None	None

Antiemetics Update

- What's new with 5-HT3 Antagonists?
- What's new with NK1 Antagonists?
- Unmet needs and Challenges

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Comparison of 5-HT₃ Antagonists

	Affinity for 5-HT ₃ Receptors (pKi)	Half-life (hours)	Generation Classification
Ondansetron (Zofran®)	8.39	4-6	First
Granisetron (Kytril®)	8.91	5-8	
Tropisetron (Navoban®)	8.81	7	
Palonosetron (Aloxi®)	10.5	40	Second



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9. Seasick Patch for Cancer Patients

By ALICE PARK Monday, Nov. 03, 2008



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convenient. Once on, the Sancuso patch quells nausea and vomiting for about five days.

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Those motion-sickness patches can really help calm a churning stomach on a boat. So, someone decided to apply the same idea to deliver anti-nausea drugs to cancer patients after chemotherapy. In September, the FDA approved Sancuso, a patch that releases a continuous dose of the drug granisetron, which blocks serotonin receptors and reduces queasiness. The prescription drug is already available to cancer patients in solution, tablet or injection form, but the patch makes delivery easier and more

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Novel Delivery of Granisetron

Goal: To improve the delivery of 1st gen 5-HT₃A

Transdermal Granisetron (Sancuso®)

- Directions: Apply one patch 24-48 hours before chemotherapy
- Continuous granisetron into the systemic circulation for up to 7 days



Sustained Release Granisetron

- Delivered by a single subcutaneous granisetron injection in the abdomen
- Delivery up to 5 days

Meta-Analysis of Efficacy of 5-HT₃ Antagonists in Prevention of Delayed Emesis from Chemotherapy

5-HT₃ A as monotherapy (versus placebo)

Benefit of 5-HT₃ A for delayed emesis

NNT **12.2** No. of doses per protected pt: 74.4

5-HT₃ A as adjunct to dexamethasone (versus dex alone)

Benefit of 5-HT₃ A for delayed emesis

NNT **38.8** No. of doses per protected pt: 423

Conclusions for DELAYED EMESIS:

-5-HT₃ A alone may not be adequate

-5-HT₃ A is not necessary if steroids are given

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Fosaprepitant (Ivemend®)

- Aprepitant prodrug
- Approved January 2008
- FDA approved dosing:
 - Fosaprepitant 115 mg IV on day 1, followed by aprepitant 80 mg PO days 2 and 3
- IV dosing on days 2 and 3
 - *No published data*
 - Roughly 50 mg IV = 80 mg PO dose

Single Dose NK1 Antagonist

- Original clinical trial has demonstrated the efficacy of single dose 285 mg aprepitant

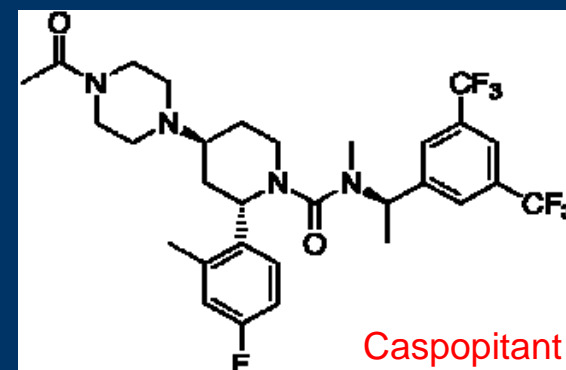
Trial, Year	N	Design	Chemotherapy	Anti-Emetics	Outcome
Grunberg et al, 2009	41	Single arm, Phase II	Doxorubicin 40 mg/m ² and or Cyclophosphamide	Aprepitant 285 mg, Dexamethasone 20 mg, Palonosetron 0.25 mg, All on D1 only	CR=51%
Herrington et al, 2007	75	Randomized, Double Blinded Control led Trial	Cisplatin > 50 mg/m ² or Doxorubicin based regimens	Dexamethasone 12 mg D1 Palonosetron 0.25 mg D1 (A) A 125 D1, 80 D2 & 3 (B) A 125 D1 only (C) Placebo	(A) CR=55.6% (B) CR=51.9% (C) CR=31.2%

A=Aprepitant; Complete Response (CR)= No vomiting/retching and No rescue medicine

- Single day fosaprepitant – Ongoing studies

Casopitant (Rezonic™ / Zunrisa™)

- NK1 receptor antagonist
- *Single dose casopitant versus 3 days dosing*
- Pharmacokinetic \leftrightarrow Safety Issues
 - Increased risk of QT prolongation
 - Increased risk of neutropenia when administered with vinorelbine and etoposide
- Application withdrawn by GSK in October 2009



Antiemetics Update

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Who will suffer from CINV?

RESEARCH REPORTS

Oncology

Clinical Predictors of Chemotherapy-Induced Nausea and Vomiting in Breast Cancer Patients Receiving Adjuvant Doxorubicin and Cyclophosphamide

Vivianne Shih, Hee Siew Wan, and Alexandre Chan

Breast cancer is the most common malignancy among women worldwide, and systemic chemotherapy is frequently offered as a treatment modality. Patients who are eligible for systemic adjuvant chemotherapy often receive anthracycline-containing regimens that have been proven, in clinical trials, to reduce disease recurrence and improve survival outcome.¹ Anthracycline-containing combination regimens such as doxorubicin and cyclophosphamide (AC); fluorouracil, epirubicin, and cyclophosphamide; and fluorouracil, doxorubicin, and cyclophosphamide are contemporary ex-

BACKGROUND: Patients with breast cancer often receive emetogenic anthracycline-based chemotherapy as part of their treatment. Chemotherapy-induced nausea and vomiting (CINV) has been commonly reported as one of the distressing adverse effects among patients with cancer. Despite the advent of newer antiemetics and better understanding of the CINV pathophysiology, total eradication of CINV has yet to be achieved.

OBJECTIVE: To assess the incidence of nausea and vomiting in patients who have breast cancer and are receiving adjuvant doxorubicin and cyclophosphamide (AC) bolus chemotherapy, ascertain patients' risk factors affecting CINV response, and study patient adherence to delayed antiemetics.

METHODS: This was a single-institution, prospective, observational study conducted at an outpatient cancer center in Singapore from December 2006 to December 2007. Clinical events such as CINV were collated using a standardized diary. Use of rescue antiemetics and unscheduled clinic visits due to CINV were documented.

RESULTS: Of a total of 106 participants, 16 patients were lost to follow-up and 1

Characteristics of patients receiving AC (N=91)

		Motion Sickness		History of Chemotx Induced nausea	
		No	89%	No	11%
		Yes	11%	Yes	89%
Age, years					
<50	52%				
>50	48%				
		Morning Sickness		History of Chemotx Induced vomiting	
		No	60%	No	29%
		Yes	36%	Yes	71%
		NA	3%		
Race					
Chinese	90%				
Malay	5%				
Indian	2%				
Other	2%				
		Anxiety		Alcohol Usage	
		No	59%	None	90%
		Yes	41%	Social	10%

How do Asians Measure Up?

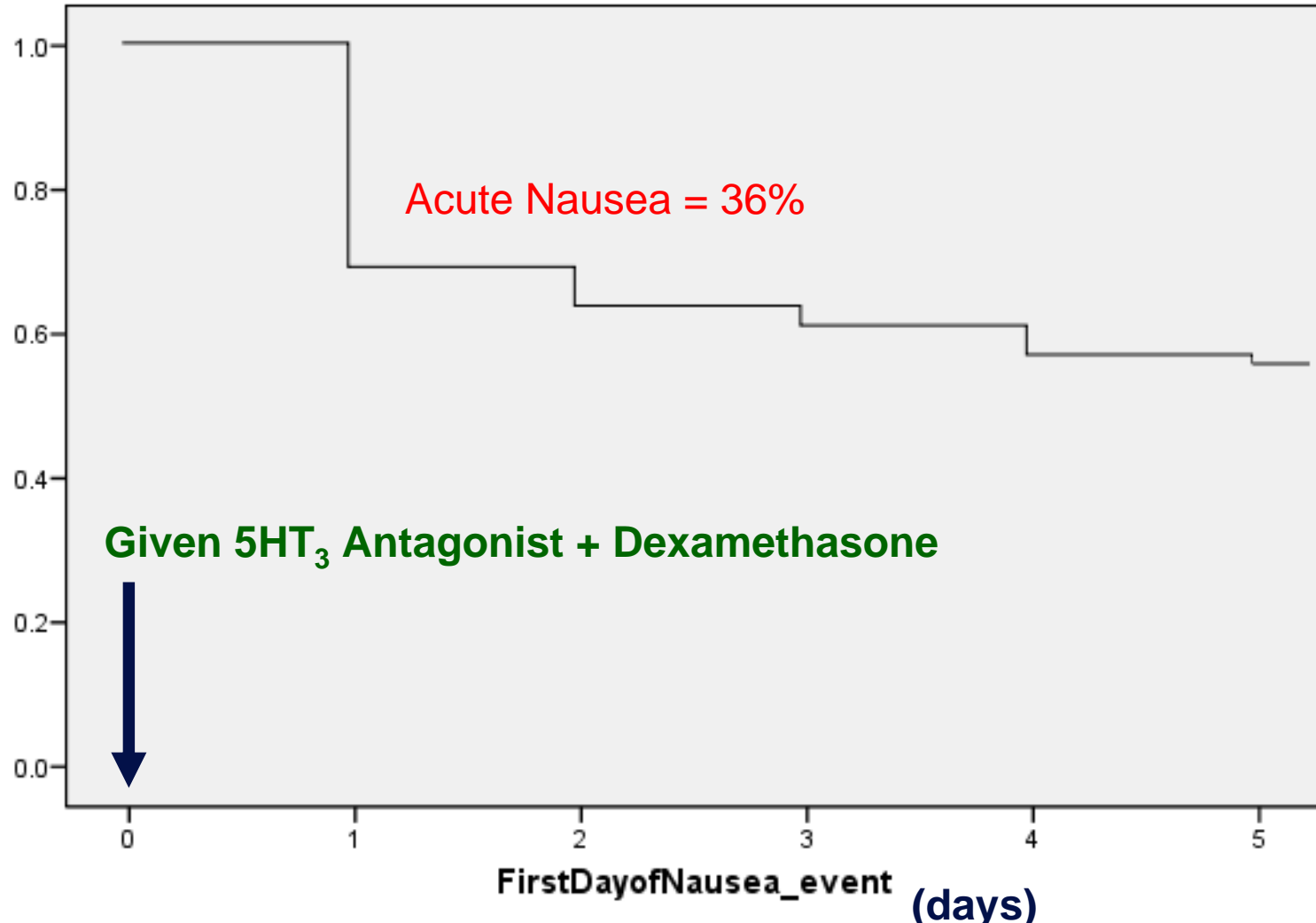
	Warr et al (N=856)	Chan et al (N=244)	
	Overall Emesis	Acute Emesis	Delayed Emesis
Predictors	<i>p</i> value	<i>p</i> value	<i>p</i> value
Young age	0.006	0.02	NS
Alcohol History (+)	0.0048	NS	NS
Morning Sickness (+)	0.0007	NS	NS
Motion Sickness (+)	NS	0.02	0.02
History of chemotherapy-induced emesis	NA	0.02	0.04

Another Challenge

- XELOX or CapeOX or CapOX
 - Gaining much popularity for treatment of various malignancies, including colorectal cancer, stomach cancers, etc
 - At NCC, patients receiving this regimen routinely receives:
 - 5HT₃ Antagonist
 - Dexamethasone
- } Prior Chemotherapy

Onset of nausea with XELOX (n=77)

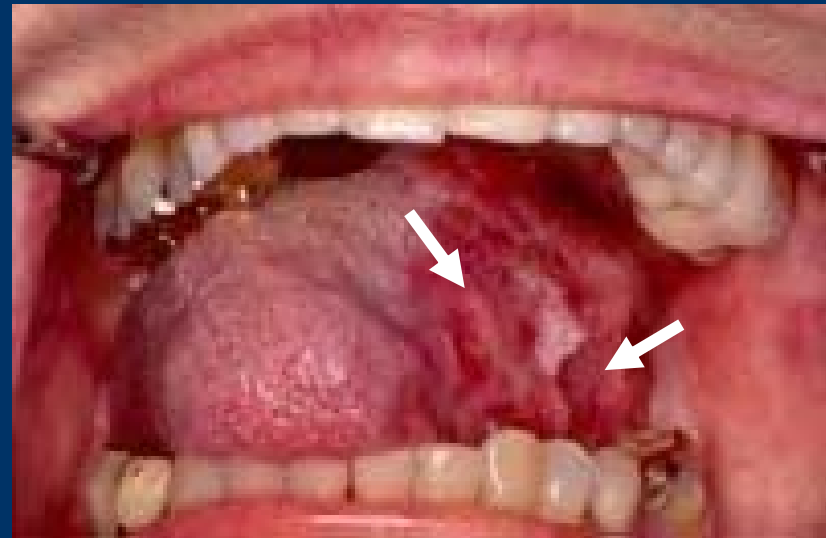
Proportion of patients free from emesis



Key points on CINV

- No additional benefit of 5-HT3 Antagonists, in combination with steroids, to prevent delayed emesis
- Novel delivery of current agents may improve CINV
- Multiple challenges still remain to optimize the management of CINV

Chemotherapy Induced Oral Mucositis (CIOM)



Challenges in CIOM management

- Often being conceived as 'inevitable'
- Guideline is available, but not widely applied
- Major determinant = Underlying oral hygiene
- Strategies are geared towards prevention
- Lacks well-designed trials



'Evidence Based' Preventive Options

- Benzydamine (Difflam®)
 - Anti-inflammatory
 - Prevention of radiation induced mucositis
- Amifostine
 - Prevention of radiation induced mucositis
- Cryotherapy
 - Often administered as ice chips or crushed ice
 - Preventive strategy for prevention of oral mucositis in patients receiving bolus 5-FU chemotherapy
- Palifermin
 - To decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies, receiving myelotoxic therapy requiring hematopoietic stem cell support: preventive



Palifermin (Kepivance®)

- Recombinant Keratinocyte Growth Factor (KGF)
- Indication: to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies, receiving myelotoxic therapy requiring hematopoietic stem cell support
- Now in guideline (Level 1 recs)



Current Evidence: Palifermin

Study	Chemo, Population	Intervention	Mucositis Outcome
Spielberger R et al, 2004 (Phase 3)	Autologous SCT (Etop+Cy+TBI)	Palifermin 60 mcg/kg/d IV or placebo, 2 days before and 3 days after SCT	↓ Mucositis severity
Rosen LS et al, 2006 (Phase 3)	5-FU 425 mg/m ² /d X 5 days + 20 mg/m ² /d leucovorin in colorectal cancer patients	Palifermin 40 mcg/kg IV or placebo prior to chemotherapy	↓ Mucositis severity
Brizel DM et al, 2008 (Randomized Phase 2)	PF (cisplatin 20 mg/m ² /d X 4d+ 5-FU 1 g/m ² /d X 4d) in head and neck cancer patients	Palifermin 60 mcg/kg/d or placebo, once weekly for 10 doses	Mucositis duration unchanged: 6.5 wks palifermin vs. 8.1 wks placebo (<i>p</i> =0.157)

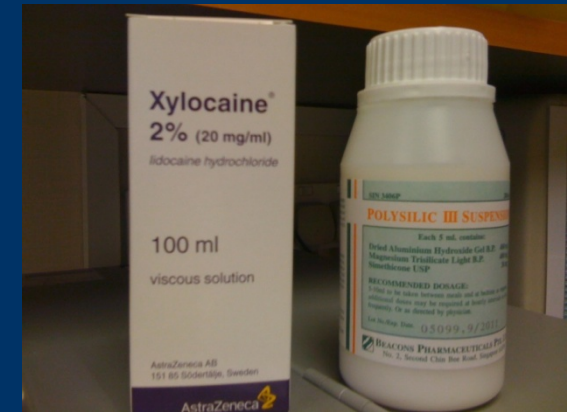
'Unendorsed' Alternatives

Preventive

- Chlorhexidine
- Sodium Bicarbonate
- Sucralfate

Treatment

- 2% Viscous Lidocaine
- Corticosteroids
- "Magic" Mouthwashes
 - 1:1:1 (Benzydamine/Diphenhydramine, Maalox®, 2% viscous lidocaine)
 - 1:2 (Xylocaine and Antacid)



Key points on CIOM

- Conflicting evidence exists for the management of CIOM
- Current research is focusing on the role of recombinant KGF to manage oral mucositis

Chemotherapy Induced Peripheral Neuropathy (CIPN)

Injury, or degeneration of the peripheral nerve fibers (motor, sensory, autonomic) caused by certain neurotoxic chemotherapy

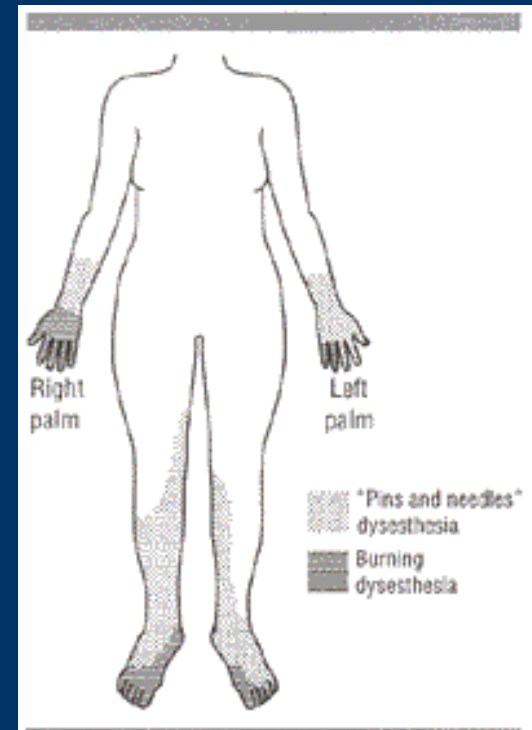
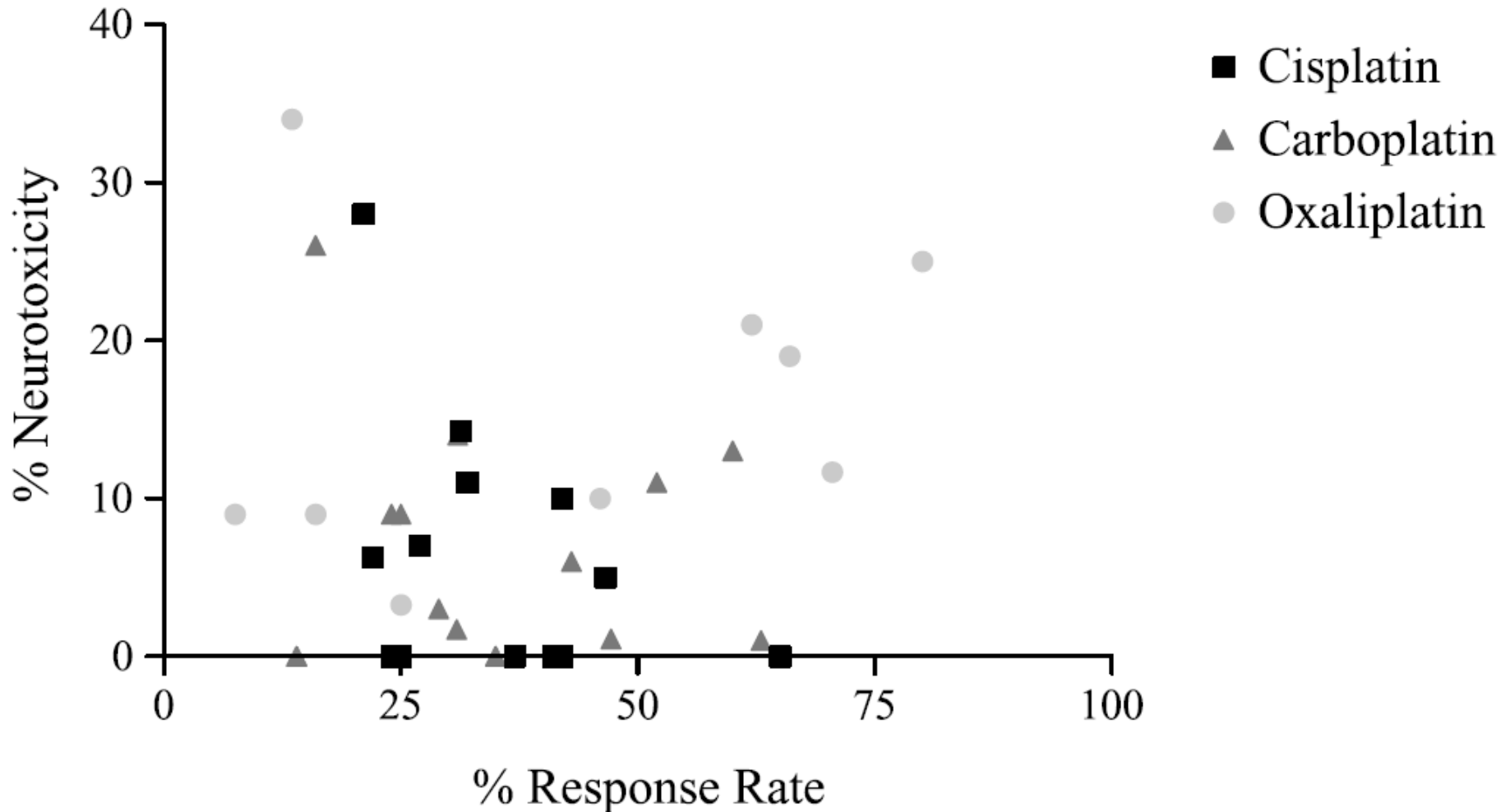


FIGURE 1. PAINFUL PERIPHERAL NEUROPATHY, SHOWING "STOCKING-GLOVE" PATTERN ON LOWER LEGS AND ARMS, AND THE CHARACTERISTIC BURNING PAIN DISTALLY AND "PINS AND NEEDLES" PROXIMALLY

Note. From *Pain: Clinical Manual* (p. 577) by M. McCaffery and C. Pasero, 1999, St. Louis, MO: Mosby. Copyright 1999 by Mosby, Inc. Reprinted by permission.

Platinum-based Chemotherapy Drug Response Rate vs. Neurotoxicity



Challenges in CIPN management

- Neurobiology poorly understood
- Prevalence unclear
- Inconsistent terminology and assessment
 - Neuropathy vs. Pain
- Lack of effective, protective agents

RCTs for prevention of CIPN

Agent / Author	N	Chemotherapy	Design	CIPN Results
Vitamin E				
Pace 2003	47	Cisplatin	OL	31% (Vit E) vs 86% (p<0.01)
Argyriou 2005	40	Cisplatin/Paclitaxel	OL	25% (Vit E) vs 73.3% (p<0.019)
Argyriou 2006	35	Cisplatin	OL	21% (VitE) vs 66% (p=0.026)
Pace 2007	81	Cisplatin	PC, DB	CIPN score is lowered (p<0.05)
Glutamine				
Wang 2007	86	Oxaliplatin	OL	Reduced CIPN after 4-6 cycles
Glutathione				
Cascinu 2002	52	Oxaliplatin	PC, DB	Less neuropathy at cycles 4 & 8
Smyth 1997	152	Cisplatin	PC, DB	Significantly decreased at cycle 8
N-acetylcysteine				
Lin 2006	14	Oxaliplatin	PC	Less in NAC arm (p<0.05)
Xaliproden				
Cassidy 2006	649	Oxaliplatin	PC, DB	17% vs 11% (Grade 3 CIPN) No reduction with overall incidence

Calcium and Magnesium Infusion

- Strategy: Ca gluconate 1 gm + Mg Sulfate 1.5 gm – before and after **oxaliplatin**
- CONcePT trial – study was terminated based on preliminary data analysis (2007)
 - Patients received Ca²⁺ and Mg²⁺ had poorer cancer treatment outcomes
 - New analysis (2008) refuted this conclusion
- Prospective data in Singapore: No difference comparing to placebo (n=27)

Pharmacogenomics of CIPN

Authors	Gene(s)	N	Tumor Type	Therapy	Neurotoxicity Relationship
Lecomte T et al., 2006	GSTP1	90	GI cancers (majority colorectal)	Various FOLFOX regimens	GSTP1-105 homozygous is associated with higher grades of neurotoxicity ($p=0.03$)
Marsh et al., 2007	ABCB1, ABCC1, ABCC2, CYP1B1, CYP2C8, CYP3A4, CYP3A5, ERCC1, ERCC2, GSTP1 , MAPT, MPO, TP53, XRCC1	914	Advanced Ovarian CA	Carboplatin + paclitaxel or docetaxel	GSTP-105 homozygous is associated with higher incidents of neurotoxicity ($p=0.018$)
Ruzzo et al., 2007	GSTP1	166	Advanced colorectal cancer	FOLFOX	GSTP1-105 homozygous are associated with higher grades of neurotoxicity ($p<0.001$)

Key points on CIPN

- CIPN is a major dose limiting side effect of many commonly used chemotherapeutic agents
- A pharmacogenomic approach may be an innovative strategy for predicting patients who will be at risk for severe neuropathy

Conclusions

- With appropriate pharmacological and non-pharmacological strategies, side effects of cytotoxic agents are highly manageable.
- Challenges still remain with the management of side effects due to chemotherapy, despite the advancement of supportive care research
- Supportive care of cancer patients should undertake a multidisciplinary approach.