MANAGING CHEMOTHERAPY SIDE EFFECTS

REVIEWING PREVENTION AND TREATMENT STRATEGIES OF THREE COMMON ISSUES

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OBJECTIVES

- Identify tactics for preventing and treating acute infusion reactions
- Describe non-pharmacological and pharmacological ways to prevent or manage chemotherapy induced peripheral neuropathy
- Demonstrate an understanding of cancer-related fatigue and treatable contributing factors

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INFUSION RELATED REACTION (IRR) HYPERSENSITIVITY REACTION (HSR)

Acute (<1 hour)

- Pruritis (itching)
- Flushing
- Urticaria (hives)
- Dyspnea
- Bronchospasm
- Chest pain/tightness
- Fever
- Rigors or chills
- Hypo- or hypertension
- Back pain

Ann Oncol. 2012;23 Suppl 10:x313-x319

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MEDICATIONS COMMONLY ASSOCIATED WITH ACUTE INFUSION REACTIONS

- TAXANES
  - PACLITAXEL (TAXOL®)
  - NAB-PACLITAXEL (ABRAXANE®)
  - DOCETAXEL (TAXOTERE®)
- PLATINUM-BASED
  - CISPLATIN (PLATINOL®)
  - CARBOPLATIN (PARAPLATIN®)
  - OXALIPLATIN (ELOXATIN®)
- CETUXIMAB (ERIBITUX®)
- RITUXIMAB (RITUXAN®)

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INFUSION RELATED REACTIONS (IRR) SUBTYPES

Type I

- Ige mediated
- Associated with repeated exposure
- Release of histamine, prostaglandins, leukotrienes
- Contraction of smooth muscle and dilation of capillaries
- Urticaria, hypotension, rash, bronchospasm

Anaphylactoid or Pseudoallergy

- First or second exposure
- Direct interaction with mast cells and basophils
- Cytokine release
- Hypotension, rash, bronchospasm

Oncologist. 2007;12(5):601-609

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COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) VERSION 5.0

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					

Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Publish Date: November 27, 2017

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EXAMPLE OF EMERGENCY ORDER SET

NURSING OXYGEN ORDERS / INSTRUCTIONS- OXYGEN DEVICE: NASAL CANNULA LITERS PER / MINUTE: 2 KEEP SPO2 > OR = TO: 92 FOR GRADE 2 - MODERATE SYMPTOMS AND GRADE 3 - SEVERE/ANAPHYLAXIS SYMPTOMS

SODIUM CHLORIDE (NS) 0.9 % INFUSION 20 ML/HR, INTRAVENOUS- FOR GRADE 1 - MILD SYMPTOMS OR GRADE 2 - MODERATE SYMPTOMS

SODIUM CHLORIDE 0.9% (NS BOLUS) BOLUS 1,000 ML- FOR GRADE 3 - SEVERE/ANAPHYLAXIS SYMPTOMS.

DIPHENHYDRAMINE (BENADRYL) INJECTION 25 MG 25 MG, INTRAVENOUS, ONCE AS NEEDED, FOR GRADE 1 - MILD SYMPTOMS, GRADE 2 - MODERATE SYMPTOMS, OR GRADE 3 - SEVERE/ANAPHYLAXIS SYMPTOMS.,

FAMOTIDINE IV 20 MG- FOR GRADE 2 - MODERATE SYMPTOMS OR GRADE 3 - SEVERE/ANAPHYLAXIS SYMPTOMS.

MEPERIDINE (DEMEROL) INJECTION 25 MG- ONCE AS NEEDED, RIGORS, STARTING WHEN RELEASED, FOR 1 DOSE FOR GRADE 1 - MILD SYMPTOMS OR GRADE 2 - MODERATE SYMPTOMS

METHYLPREDNISOLONE SODIUM SUCCINATE INJECTION 125 MG- 125 MG, INTRAVENOUS, ONCE AS NEEDED, FOR GRADE 2 - MODERATE SYMPTOMS OR GRADE 3 - SEVERE/ANAPHYLAXIS SYMPTOMS.

EPINEPHRINE IM 0.3 MG- 0.3 MG, INTRAMUSCULAR, ONCE AS NEEDED, FOR GRADE 3 - SEVERE/ANAPHYLAXIS SYMPTOMS

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TAXANES

PACLITAXEL (TAXOL®)	NAB-PACLITAXEL (ABRAXANE®)	DOCETAXEL (TAXOTERE®)
SOLVENT: CREMEPHOR EL (POLYOXYL 35/POLYOXYETHYLATED CASTOR OIL)	SOLVENT: N/A	SOLVENT: POLYSORBATE 80 (TWEEN 80)
PREMEDICATION: H1 BLOCKER, CORTICOSTEROID, H2 BLOCKER	PREMEDICATION: NO PREMEDICATION IS REQUIRED	PREMEDICATION: CORTICOSTEROID FOR 3 DAYS; DEXAMETHASONE 8 MG TWICE DAILY, BEGIN DAY BEFORE INFUSION
RATE OF HSR: 31-45%; SEVERE: 2-4%	RATE OF HSR: 4%	RATE OF HSR: 6-21%
CROSS REACTIVITY: ??	CROSS REACTIVITY: RARE	CROSS REACTIVITY: ??

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PACLITAXEL (AND DOCETAXEL): RE-CHALLENGE

- INCREASE CORTICOSTEROIDS
  - DEXAMETHASONE 20 MG PO 12 HOURS AND 6 HOURS PRIOR
- INCREASE ANTIHISTAMINES
- SLOW INFUSION RATE
  - 50% OF USUAL RATE
  - TITRATION

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TOLERANCE OF NAB-PACLITAXEL

37 patients	All doses appropriately premedicated	Nab-paclitaxel
• 31 history of paclitaxel HSR • 6 history of paclitaxel and docetaxel hsr	• Paclitaxel-Dexamethasone 20mg iv, diphenhydramine 50 mg iv, famotidine 20 mg iv (30 minutes before) • Docetaxel-dexamethasone 20 mg po (evening before and morning of), diphenhydramine 50 mg iv, famotidine 20 mg iv (30 minutes before)	• Dexamethasone 10 mg iv (30 minutes before) first 3 infusions • Dexamethasone omitted unless needed for nausea prevention • No HSRs

J Gynecol Oncol. 2017;28(4):e38

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PLATINUM-BASED CHEMOTHERAPIES AND HSRS

- PRIMARILY IGE MEDIATED
- OCCURRENCE INCREASES WITH INCREASED EXPOSURE
- INCREASE IN SEVERITY
- NOT IMMEDIATELY RESPONSIVE TO TREATMENT

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RITUXIMAB

Dermatologic	• Pruritis ≤ 17% • Urticaria 2-8%
Respiratory	• Dyspnea 7-10% • Bronchospasm 8%
Cardiovascular	• Flushing 5-14% • Hypertension 6-12% • Hypotension 10% • Chest tightness 7%
Other	• Angioedema 11% • Rigors 10%

Rituximab (intravenous) including biosimilars of rituximab: Drug Information: LexiComp.In: *UpToDate*. Waltham, Mass.: UpToDate; 2020. www.uptodate.com. Accessed August 1,2020.

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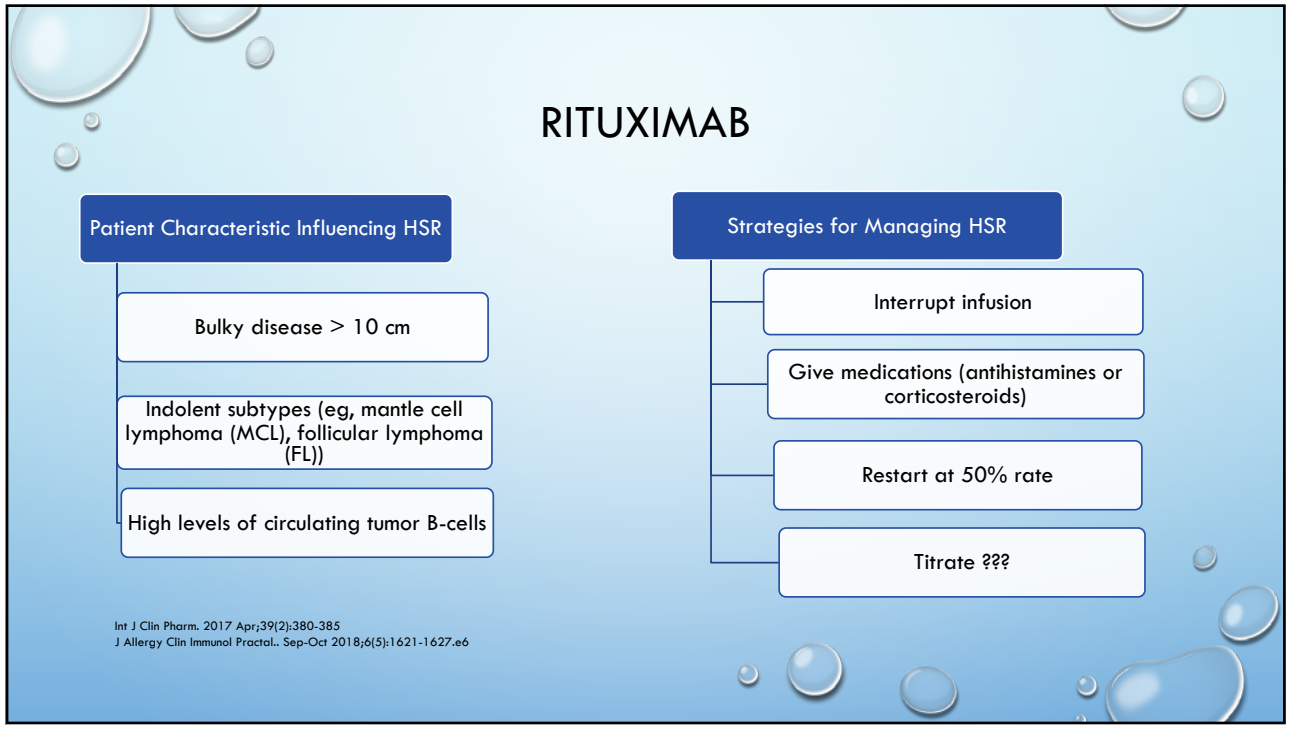
RITUXIMAB
Patient Characteristic Influencing HSR
Bulky disease > 10 cm
Indolent subtypes (eg, mantle cell lymphoma (MCL), follicular lymphoma (FL))
High levels of circulating tumor B-cells
Strategies for Managing HSR
Interrupt infusion
Give medications (antihistamines or corticosteroids)
Restart at 50% rate
Titrate ???
Int J Clin Pharm. 2017 Apr;39(2):380-385
J Allergy Clin Immunol Practal.. Sep-Oct 2018;6(5):1621-1627.e6

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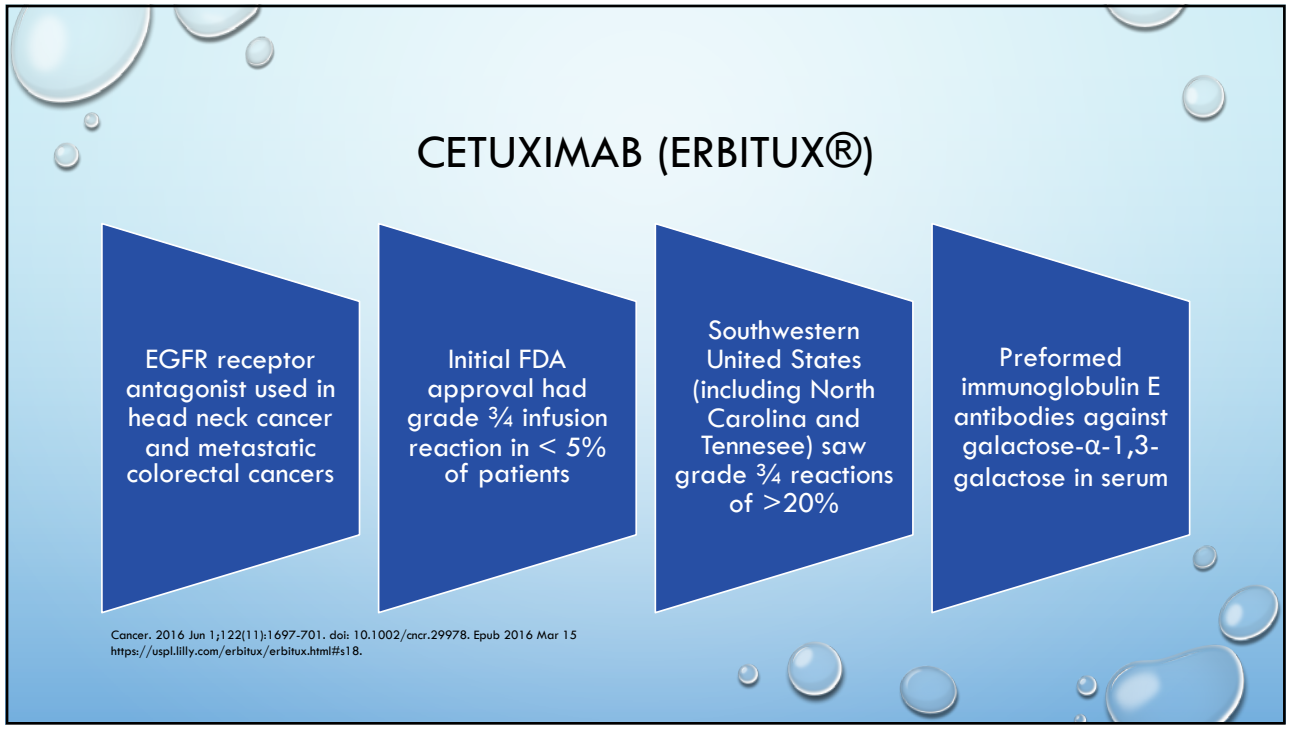
CETUXIMAB (ERBITUX®)
EGFR receptor antagonist used in head neck cancer and metastatic colorectal cancers
Initial FDA approval had grade ¾ infusion reaction in < 5% of patients
Southwestern United States (including North Carolina and Tennesee) saw grade ¾ reactions of >20%
Preformed immunoglobulin E antibodies against galactose-α-1,3-galactose in serum
Cancer. 2016 Jun 1;122(11):1697-701. doi: 10.1002/cncr.29978. Epub 2016 Mar 15
https://uspl.lilly.com/erbitux/erbitux.html#s18.

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CETUXIMAB

Alpha-gal assay for IgE antibodies
- Negative = < 0.10 kU/L
- Included levels up to <0.35 kU/L

Alpha-gal testing not mandated in package insert
- Evaluate for history of tick bites
- History of red meat allergy

61.7% (37/60) patients negative
- Values: <0.10-0.23 kU/L
- No anaphylaxis

Send out test
- 7 days for results

38.3% (23/60) patients positive
- Values: <1.0-44.2
- Excluded from cetuximab arm

Premedicate
- Antihistamines
- Corticosteroids

Cancer. 2016 Jun 1;122(11):1697-701.
https://uspl.lilly.com/erbitux/erbitux.html#s18.

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RAPID DRUG DESENSITIZATION

➢ ONE SOLUTION DESENSITIZATION
- TOTAL DOSE PREPARED
- 500 ML TOTAL VOLUME- PLATINES, TAXANES, RITUXIMAB
- 250 ML FOR CETUXIMAB

➢ PREMEDICATIONS
- CETIRIZINE 10 MG ORAL (PO)- (EVERY 12 HOURS SINCE 3 DAYS BEFORE)
- ASPIRIN 200-500 MG PO - (EVERY 24 HOURS SINCE DAY BEFORE, UNLESS CONTRAINDICATION)
- MONTELUKAST 10 MG PO - (EVERY 24 HOURS SINCE DAY BEFORE)
- DEXCHLORPHENIRAMINE 5 MG IV – (30 MINUTES BEFORE)
- RANITIDINE 50 MG IV – (30 MINUTES BEFORE)
- METHYLPREDNISILONE 1 MG/KG IV OR HYDROCORTISONE 100 MG IV FOR RITUXIMAB
- DEXAMETHASONE 20 MG PO (12 HOURS AND 1 HOUR BEFORE)

J Allergy Clin Immunol Pract. 2018;6(5):1621-1627.e6.

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RAPID DRUG DESENSITIZATION

Example of dosing for 130 mg of oxaliplatin diluted in 525 mL of volume (0.247 mg/mL)						
Rate (mL/hr)	Time (min)	Accumulated Time (min)	Volume (mL)	Accumulated Volume (mL)	Dose (mg)	Accumulated Dose (mg)
5	15	15	1.25	1.25	0.3	0.3
10	15	30	2.5	3.75	0.68	0.98
25	15	45	6.25	10	1.54	2.52
50	15	60	12.5	22.5	3.08	5.6
75	15	75	18.75	41.25	4.63	10.23
100	15	90	25	66.25	6.17	16.4
150	15	105	37.5	103.75	9.26	25.66
200	15	120	50	153.75	12.35	38.01
250	89.16	209.16	371.5	525	91.76	129.77

J Allergy Clin Immunol Pract. 2018;6(5):1621-1627.e6

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TAKE HOME POINTS

- HYPERSENSITIVITY REACTIONS/INFUSION RELATED REACTIONS ARE UNPREDICTABLE
- PREDICTING IRRS MAY BE POSSIBLE IN CETUXIMAB AND RITUXIMAB
- HAVE STANDING HSR RESPONSE ORDERS IN PLACE
- CONSIDER ENHANCED PREMEDICATION STRATEGIES AND SLOWER INFUSION RATES
- DISCONTINUE PRECIPITATING MEDICATION
- CHANGE TREATMENT WHERE APPROPRIATE
- CONSIDER DESENSITIZATION WHEN DISCONTINUATION OR CHANGING TREATMENT NOT OPTION AND/OR EXPECTED FUTURE TREATMENTS ARE LIMITED

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CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY (CIPN)

RECOMMENDATIONS FOR PREVENTION AND TREATMENT

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CHEMOTHERAPY AGENTS ASSOCIATED WITH PERIPHERAL NEUROPATHY

- TAXANES
- PLATINUMS
- VINCA ALKALOIDS
- ERIBULIN
- BORTEZOMIB/CARFILZOMIB

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PREVENTION AND MANAGEMENT OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY IN SURVIVORS OF ADULT CANCERS: AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) GUIDELINE UPDATE

- PACLITAXEL MYALGIAS AND ARTHRALGIAS RECLASSIFIED AS ACUTE NEUROPATHY
- TOTAL CHEMOTHERAPY EXPOSURE ONLY RECOMMENDED PREVENTION STRATEGY

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ASCO CIPN UPDATE: PREVENTION

NOT RECOMMENDED: POTENTIALLY HARMFUL

- Acetyl-l-carnitine

RECOMMENDED IN CLINICAL TRIAL: REQUIRES MORE DATA

- Acupuncture
- Cryotherapy
- Compression therapy
- Exercise therapy
- Ganglioside-monosialic acid (GM-1)

NOT RECOMMENDED: NO BENEFIT FOUND

- Amitriptyline
- Calcium magnesium
- Gabapentin/pregabalin
- Omega-3 fatty acids
- Venlafaxine
- Vitamin B
- Vitamin E

ASCO Guideline Update. DOI: 10.1200/JCO.20.01399

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CRYOTHERAPY

KEEPING HANDS AND FEET COLD DURING CHEMOTHERAPY ADMINISTRATION

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CRYOTHERAPY: POTENTIAL BENEFIT

HANAI, A ET AL. 2018

- FROZEN GLOVES AND SOCKS
- PATIENTS WERE OWN CONTROLS

RUDDY, KJ ET AL. 2019

- IMPROVEMENT SHOWN WITH POOLED CONTROL GROUPS FROM OTHER STUDIES

Breast 48:89-97, 2019
J Natl Cancer Inst 110:141-148, 2018

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ASCO TREATMENT RECOMMENDATIONS

For painful neuropathy	• Duloxetine
Not recommended outside of clinical trial	• Exercise therapy • Acupuncture • Scrambler therapy • Gabapentin/pregabalin • Topical gel treatment containing baclofen, amitriptyline HCL, plus/minus ketamine • Tricyclic antidepressants • Oral cannabinoids

ASCO Guideline Update. DOI: 10.1200/JCO.20.01399

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TRICYCLIC ANTIDEPRESSANTS

Amitriptyline, nortriptyline, desipramine and imipramine

Moved from: "reasonable to try" to "not recommended"

Lack of evidence for efficacy in treating CIPN

No new clinical trials since last update

Unfavorable side effects: drowsiness, irregular heart rate, confusion in older patients

ASCO Guideline Update. DOI: 10.1200/JCO.20.01399

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GABAPENTINOIDS
GABAPENTIN AND PREGABALIN

Evidence for treating established CIPN is inconclusive	More clinical trials required before routine use endorsed by ASCO	Some insurance companies require failed trial of gabapentinoid before duloxetine

ASCO Guideline Update. DOI: 10.1200/JCO.20.01399

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PREGABALIN VERSUS DULOXETINE
BREAST CANCER PATIENTS TREATED WITH PACLITAXEL OR DOCETAXEL

Pregabalin
- 75 mg once daily x 1 week
- 150 mg twice daily x 5 weeks
- N=40
- Visual analog scale (VAS) scores improved in 37/40 (92.5%)

Duloxetine
- 30 mg once daily x 1 week
- 30 mg twice daily x 5 weeks
- N=42
- Visual analog scale (VAS) scores improved in 16/42 (38.1%)

Salehifar E et al. Clin Drug Investig. 2020 Mar;40(3):249-257. doi: 10.1007/s40261-019-00882-6.
Avan R et al. *J Res Med Sci.* 2018;23:52. doi: 10.1016/j.jaip.2017.11.013

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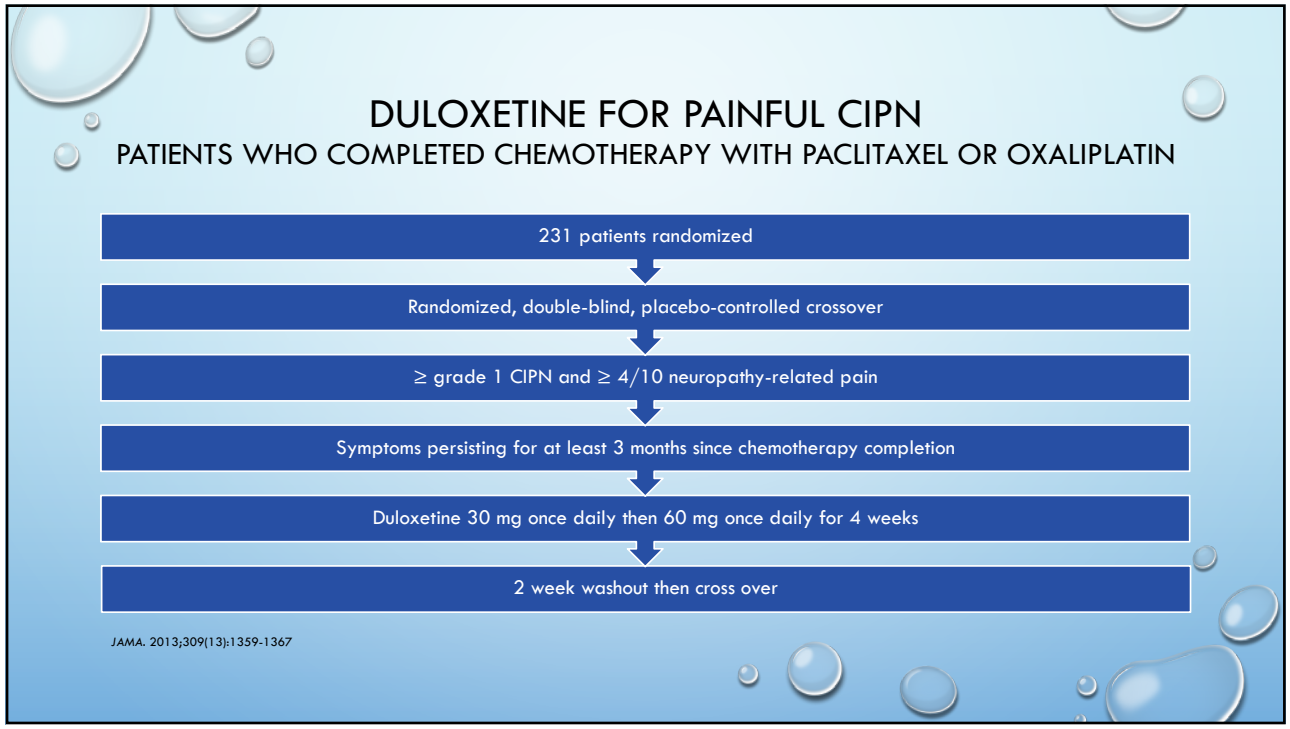
DULOXETINE FOR PAINFUL CIPN
PATIENTS WHO COMPLETED CHEMOTHERAPY WITH PACLITAXEL OR OXALIPLATIN
231 patients randomized
Randomized, double-blind, placebo-controlled crossover
≥ grade 1 CIPN and ≥ 4/10 neuropathy-related pain
Symptoms persisting for at least 3 months since chemotherapy completion
Duloxetine 30 mg once daily then 60 mg once daily for 4 weeks
2 week washout then cross over
JAMA. 2013;309(13):1359-1367

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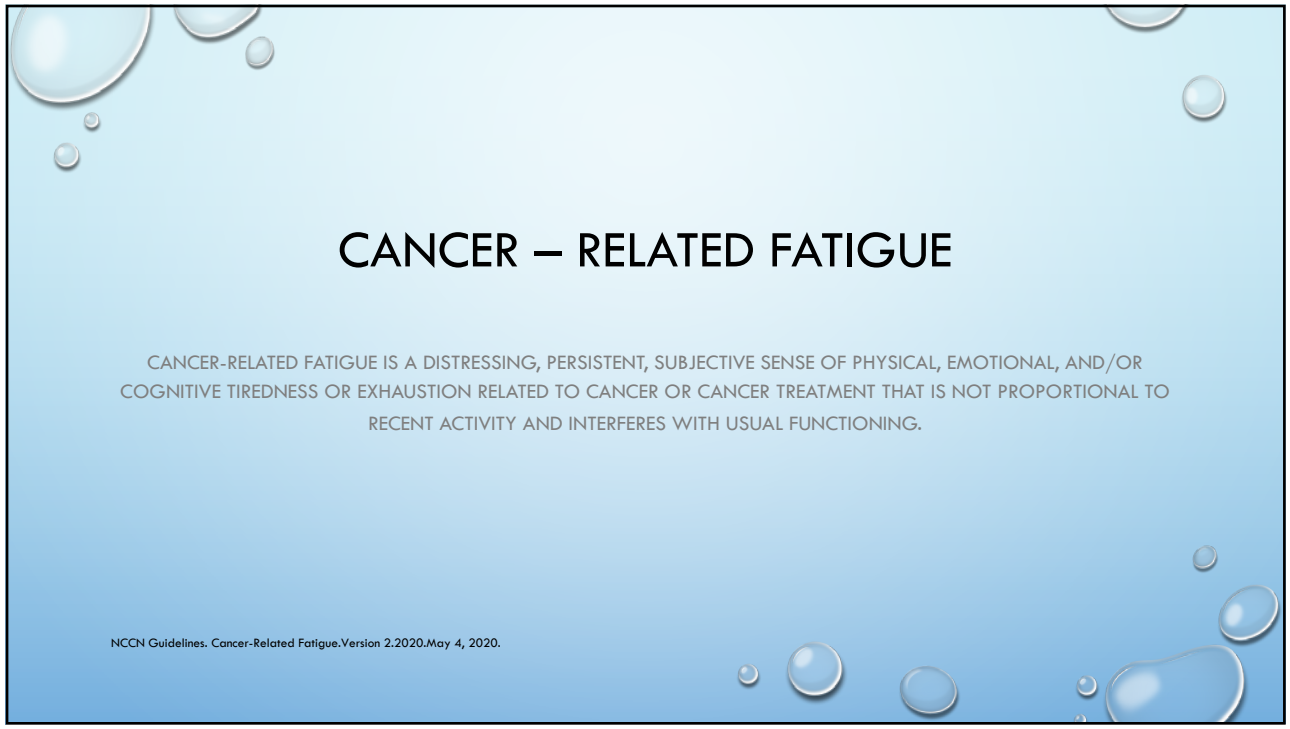
CANCER – RELATED FATIGUE
CANCER-RELATED FATIGUE IS A DISTRESSING, PERSISTENT, SUBJECTIVE SENSE OF PHYSICAL, EMOTIONAL, AND/OR COGNITIVE TIREDNESS OR EXHAUSTION RELATED TO CANCER OR CANCER TREATMENT THAT IS NOT PROPORTIONAL TO RECENT ACTIVITY AND INTERFERES WITH USUAL FUNCTIONING.
NCCN Guidelines. Cancer-Related Fatigue.Version 2.2020.May 4, 2020.

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EVALUATING AND ASSESSING FATIGUE

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relived by rest; limiting self care ADL	----	----
	Definition: A disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities.				

Common Terminology Criteria for Adverse Events (CTCAE) v5.0

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EVALUATING AND ASSESSING FATIGUE

- SCALE OF 1-10
  - 0= NO FATIGUE AND 10= WORST FATIGUE YOU CAN IMAGINE
  - 0-3= NONE TO MILD
  - 4-6= MODERATE
  - 7-10= SEVERE
- DESCRIPTION
  - NONE
  - MILD
  - MODERATE
  - SEVERE

. NCCN Guidelines. Cancer-Related Fatigue.Version 2.2020.May 4, 2020.

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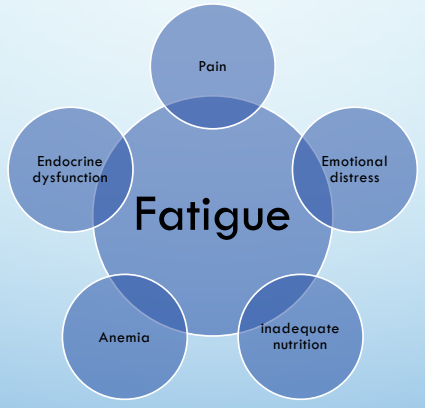
IDENTIFY AND TREAT UNDERLYING CAUSES



NCCN Guidelines. Cancer-Related Fatigue.Version 2.2020.May 4, 2020.

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INADEQUATE NUTRITION

NUTRITION CONSULT

PHARMACY

NURSING SUPPORT

- Nausea or vomiting
- Dysgeusia
- Loss of appetite
- Constipation
- Diarrhea
- Mucositis
- Gerd

NCCN Guidelines. Cancer-Related Fatigue.Version 2.2020.May 4, 2020.

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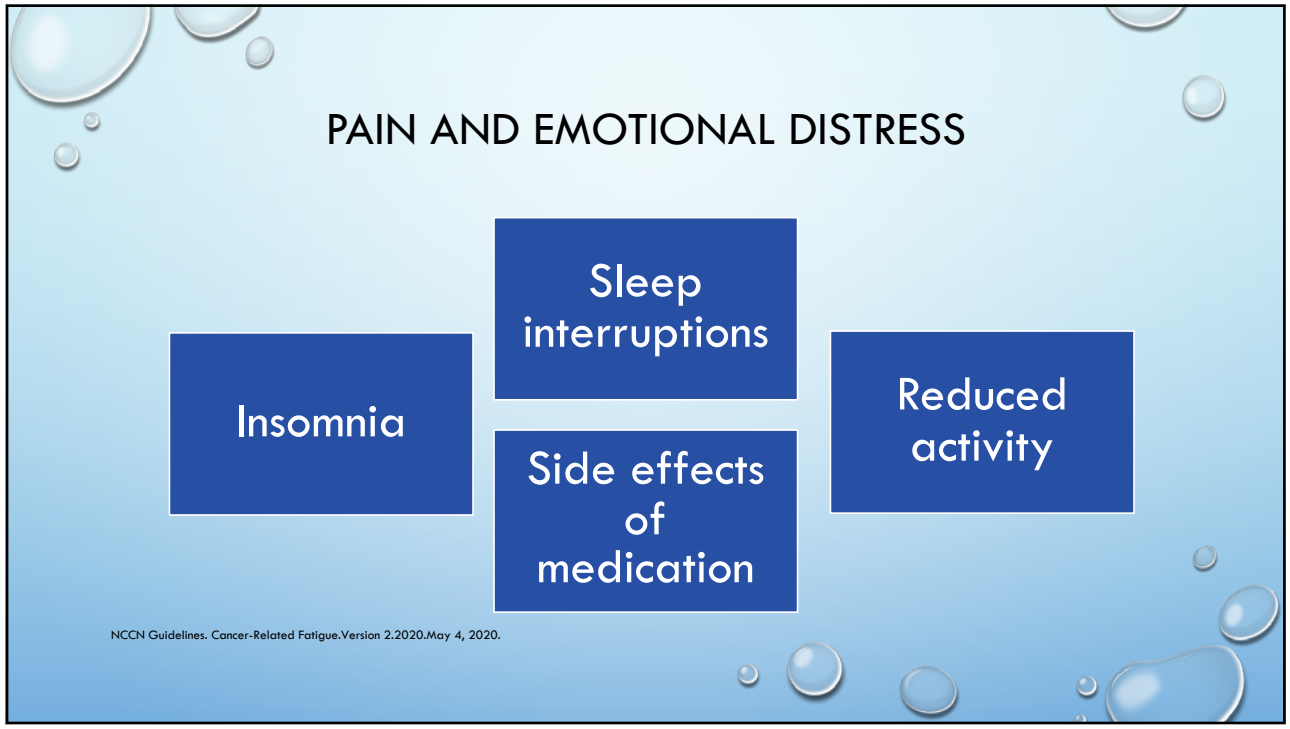
PAIN AND EMOTIONAL DISTRESS
Sleep interruptions
Insomnia
Reduced activity
Side effects of medication
NCCN Guidelines. Cancer-Related Fatigue.Version 2.2020.May 4, 2020.

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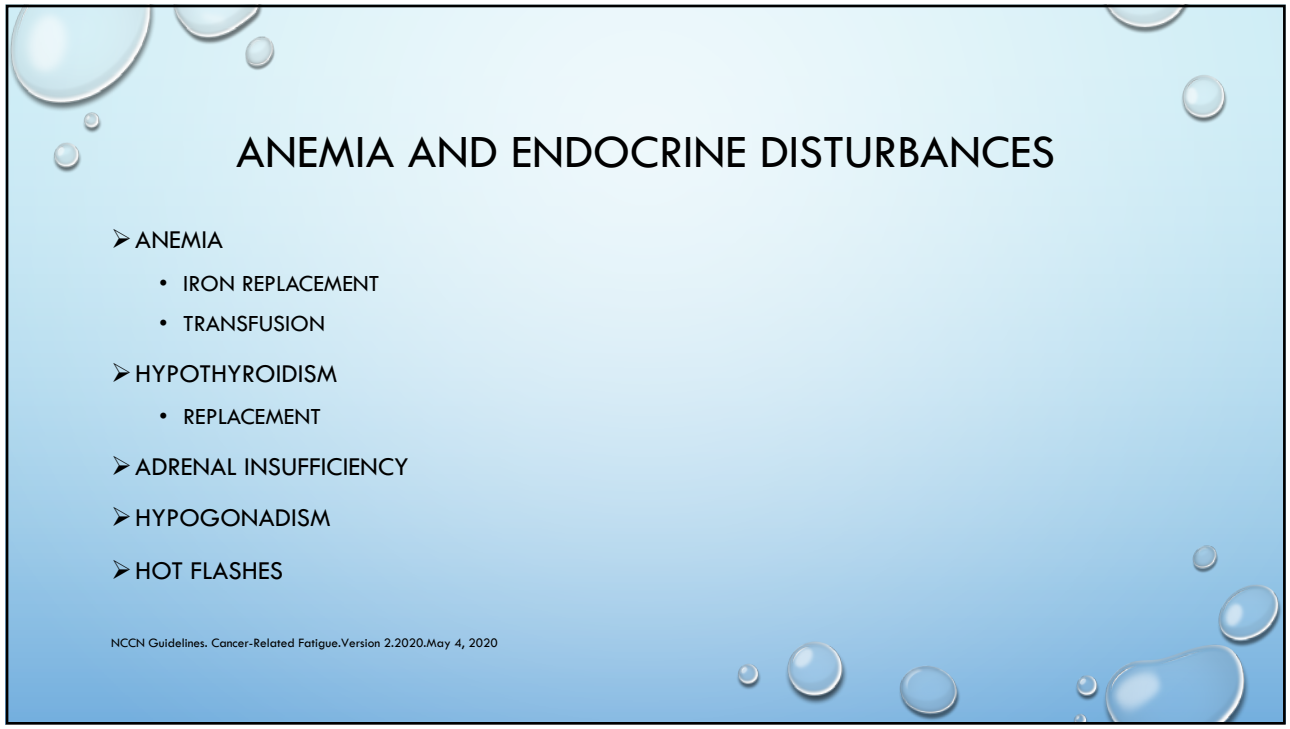
ANEMIA AND ENDOCRINE DISTURBANCES
ANEMIA
IRON REPLACEMENT
TRANSFUSION
HYPOTHYROIDISM
REPLACEMENT
ADRENAL INSUFFICIENCY
HYPOGONADISM
HOT FLASHES
NCCN Guidelines. Cancer-Related Fatigue.Version 2.2020.May 4, 2020

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NON-PHARMACOLOGICAL INTERVENTIONS

Sleep Hygiene

Avoid caffeine/nicotine in late afternoon	Consistent schedule	Avoid bright light in evenings	Turn off electronics 30 minutes before	Eat light at night

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NON-PHARMACOLOGICAL INTERVENTIONS

Physical activity	Yoga	Patient Specific Considerations
• Walk 30 minutes most days of the week • Cardiovascular endurance • Resistance training	• Twice weekly	• Bone metastasis • Thrombocytopenia/anemia • Recent surgery • Safety issues (e.g. falling)

NCCN Guidelines. Cancer-Related Fatigue.Version 2.2020.May 4, 2020.

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PHARMACOLOGICAL INTERVENTIONS

Methylphenidate
- Active treatment
- Advanced cancer
- End of life

Corticosteroids
- Short term use
- Advanced cancer

Nutritional supplements
- Inconclusive

Modafinil
- Not recommended

Antidepressants
- Not recommended

NCCN Guidelines. Cancer-Related Fatigue.Version 2.2020.May 4, 2020.

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METHYLPHENIDATE

- USE WITH CAUTION
- FIRST RULE OUT AND TREAT UNDERLYING CAUSES
- SHOWS IMPROVEMENT IN FATIGUE COMPARED TO PLACEBO
- OPTIMAL DOSING IN CANCER PATIENTS AND OLDER ADULTS NOT ESTABLISHED
  - METHYLPHENIDATE 5 MG TO 36 MG DAILY IN TRIALS
  - METHYLPHENIDATE 5 MG ONCE DAILY STARTING DOSE
- SIDE EFFECTS
  - HEADACHE
  - NAUSEA

Cancer Care (Engl). 2016;25(6):970-979
NCCN Guidelines. Cancer-Related Fatigue.Version 2.2020.May 4, 2020
J Clin Oncol. 2010 Aug 10;28(23):3673-9

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- HAYAMA T, MIURA K, UCHIIKE A, ET AL. CLINICAL PREDICTION MODEL FOR INFUSION-RELATED REACTIONS TO RITUXIMAB IN PATIENTS WITH B CELL LYMPHOMAS. INT J CLIN PHARM. 2017 APR;39(2):380-385. DOI: 10.1007/S11096-017-0429-3. EPUB 2017 JAN 31
- RITUXIMAB (INTRAVENOUS) INCLUDING BIOSIMILARS OF RITUXIMAB: DRUG INFORRMATION: LEXICOMP.IN: *UPTODATE*. WALTHAM, MASS.: UPTODATE; 2020. WWW.UPTODATE.COM. ACCESSED AUGUST 1,2020
- PÉREZ-RODRÍGUEZ E, MARTÍNEZ-TADEO JA, PÉREZ-RODRÍGUEZ N, ET AL. OUTCOME OF 490 DESENSITIZATIONS TO CHEMOTHERAPY DRUGS WITH A RAPID ONE-SOLUTION PROTOCOL.. J ALLERGY CLIN IMMUNOL PRACTAL. SEP-OCT 2018;6(5):1621-1627.E6. DOI: 10.1016/J.JAIP.2017.11.033. EPUB 2018 FEB 1.
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- CETUXIMAB PRESCRIBING INFORMATION. USPL.LILLY.COM/ERBITUX/ERBITUX.HTML#S18.
- COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) V5.0. PUBLISH DATE: NOVEMBER 27, 2017
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- HANAI A, ISHIGURO H, SOZU T, ET AL: EFFECTS OF CRYOTHERAPY ON OBJECTIVE AND SUBJECTIVE SYMPTOMS OF PACLITAXEL-INDUCED NEUROPATHY: PROSPECTIVE SELF-CONTROLLED TRIAL. J NATL CANCER INST 110:141-148, 2018DHAWAN S, ANDREWS R, KUMAR L, ET AL: A RANDOMIZED CONTROLLED TRIAL TO ASSESS THE EFFECTIVENESS OF MUSCLE STRENGTHENING AND BALANCING EXERCISES ON

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