Management of Symptom Distress in Advanced Cancers – Role of Steroids

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Making Cancer History*

COI Disclosures

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Objectives

Case presentation
Symptom distress and palliative care
Role of Steroids on symptom Distress
Conclusion

Case Presentation

Case Presentation

A.W. is a 51-yo with NSCL Ca, metastatic to lymph nodes and bone.

DAIN

- Chest wall
- Sharp and stabbing
- Radiating from the anterior chest wall to the posterior chest wall on the right side
- Increased since 2 weeks
- It is partially relieved with oxycodone and hydromorphone

Case Presentation

Additional complaints Constipation The patient's had no bowel movement for 3 days ago. Sleep walking ■ Confusion Myoclonus and hallucinations cough with white-to-clear-colored sputum.

Neoplastic History

Diagnosis 07/2004:

- Right chest and scapular pain
- CT scan Chest
 - Right hilar mass
- PET scan and bronchoscopy
 - Squamous cell carcinoma, metastatic to the right ischium.
- Stage IV
- **Chemotherapy:**
 - Cisplatinum and Paclitaxel for three cycles
 - No response
 - Palliative RT to the right hip (30gray/10;10/11/2004-11/02/2004), right lung and associated mediastinum
- Further treatment of a Pemetrexed (Alimta[®]) with further disease progression.

Psychosocial History

- Married for the second time to his wife now of 10 years.
- They each have a child from a previous marriage.
- Daughter is supportive (AIDS and cervical cancer).
- More recently he has been driving a truck with his wife, which they have greatly enjoyed.
- The patient is on disability, has a high school education.
- His wife also has liver cancer. She is on interferon and other medications for her condition.
- There have one 15-year-old grandchild in the home. This is the patient's wife's grandchild. He is having difficulty in school. He has 3 siblings who are in foster homes.
- 30 pack/year smoking and Cage 2/4



Medications Prior to Admission

- Oxycodone ER(Oxycontin) 80 mg four times a day
- Hydromorphone(Dilaudid) 12 mg four times a day
- Oxycodone 40 mg every four hours as needed
- Temezepam(Restoril) 20 mg 2 tablets nightly
- Warfarin 1 mg daily
- Paroxetine(Paxil) 40mg qhs
- Tamsulosin(Flomax) 0.4 mg daily
- Ondansetron(Zofran) 8 mg every 8 hours

10										
9					:					
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1										
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	Pain	Fatigue	Nausea	Depression	Anxiety	Drowsiness	Dyspnea	Appetite	Sleep	Well Being

Discharge Medications

- 1. Senokot- colace 2 times a day.
- 2. Paroxetine(Paxil) 20 mg daily.
- 3. Clonazepam(Klonopin) 0.5 mg 2 times a day.
- 4. Methadone 10 mg every 8 hours.
- 5. Pantoprozole 40 mg daily.
- 6. Warfarin 1 mg nightly.
- 7. <u>Dexamethasone</u> 2 mg daily for 5 days and then 2 mg every other day for 5 days.
- 8. Methadone 5 mg, 1/2 tablet every 2 hours as needed for pain.
- 9. Metaclopramide 10 mg every 2 hours per mouth as needed.

Objectives

- Symptom Distress and Advanced Cancer
- Corticosteroids and their role in Palliative Care
- Evidence for its benefits of Corticosteroids
- Side effects of Corticosteroids
- **Summary**

Symptom Distress and Palliative Care

Frequency of multiple symptoms

Walsh, et al. Supportive Care in Cancer, 2000

- Oncology patients on admission to a palliative care unit (n=1000)
- Prevalence of symptoms
 - Pain 84%
 - Easy fatigue 69%
 - Weakness 66%
 - Anorexia 66%
 - Lack of energy 61%
 - Dry mouth 57%
 - Constipation 52%
 - Early satiety 51%
 - Dyspnea 50%
 - > 10% weight loss 50%
 - Sleep problems 49%
 - Depression 41%

Frequency of Symptoms in Terminal Cancer Patients**

Symptom	TPCU	Referral hospitals	Hospices	"p" value
Pain	116/156 74 percent	300/639 47 percent	231/407 57 percent	<0.0001 **
Activity	138/154 90 percent	561/624 90 percent	356/431 83 percent	0.0014**
Nausea	55/152 36 percent	125/636 20 percent	93/368 25 percent	0.0001**
Depression	87/148 59 percent	250/573 44 percent	179/391 46 percent	0.0042**
Anxiety	102/152 67 percent	288/583 49 percent	202/403 50 percent	0.0003**
Drowsiness	111/154 72 percent	394/621 63 percent	310/417 74 percent	0.0006**
Appetite	116/152 76 percent	502/617 81 percent	314/428 73 percent	0.0082
Well being	118/147 80 percent	390/540 72 percent	262/404 65 percent	0.001**
Shortness of breath	76/153 50 percent	206/630 33 percent	151/393 38 percent	0.0004**

Symptoms were considered present when the visual analogue score upon admission was (30/100)
 ** P value significant after boferroni correction

* Reproduced with from Bruera, E, Neumann, CM. Respective limits in palliative care and oncology in the supportive care of cancer patients. Support Care Cancer 1999; 7:321.

Baseline Symptoms and laboratory characteristics

Baseline ESAS (N = 1,778)	Mean (SD); Median
Composite(Distress) score	40 (16.58); 39
Pain	5 (2.91);5
Fatigue	6 (2.39);6
Nausea	2 (2.74); 1
Depression	3 (2.87); 3
Anxiety	3 (3.00);3
Appetite	4 (3.08);4
Drowsiness	4 (3.12);5
Well Being	5 (2.72);5
Shortness of Breath	3 (2.89);2
Sleep Disturbance	5 (2.88);5
Hemoglobin ($N = 1,426$)	11 (1.82);11.3
Anemia	N = 314 (17.62%)
Albumin (N = $1,178$)	4 (0.58); 3.7
Low Albumin	N =192 (10.77%)
Delirium based on MDAS	N =31 (1.74%)
Alcoholism based on CAGE	N = 184 (10.33%)

INFLAMMATION AND CANCER RELATED SYMPTOMS



Dantzer, et al., 2004



Capuron & Miller 2011

Corticosteroids

- Commonly used to treat cancer related symptoms in palliative care patients
- Potent anti-inflammatory effect
- Acts by binding to cytoplasmic steroid hormone receptor, migrating to nucleus and modulation of inflammatory gene transcription
- Cytokines IL-6, IL-1b, TNF-alpha, PGE and dopamine
- Impacts Hypothalamic-Pituitary-Adrenal axis function
- Tumor mass, function, and tumor byproducts

Role of Steroids on symptom Distress

Medication Interventions in Outpatient Palliative Care



Fig. 2. Most frequent pharmacological interventions (either initiation, discontinuation, change of dose [either increase or decrease in the dose]) used by the palliative care consultation team (n = 403).

Corticosteroids in Palliative care

- Lundstrom& Furst Survey 2005
- 302 physicians
- Data from 1292 patients
- Corticosteroid prescription attitudes and clinical practice in Swedish palliative care

Assessed effect of corticosteroid treatment in cancer patients Lundstrom, 2005 100% Percentage of patients 80% 60%-40% 20% 0%-Appetite Fatigue Pain Poor Nausea wellbeing loss Treatment indication

Figure 1. Assessment of effect on different symptoms for cancer patients treated with corticosteroids (Survey 2).

Lundstrom et al, 2005

Side effect	No. (%)
Moon face	77 (43)
Myopathy/muscle weakness	61 (34)
Skin purpura	57 (31)
Oral candidosis	51 (28)
Aggravated/triggered diabetes mellitus	31 (17)

Objectives

- Symptom Distress and Advanced Cancer
- **Corticosteroids and their role in Palliative Care**
- > Evidence for its benefits of Corticosteroids
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REDUCTION OF CANCER-RELATED FATIGUE WITH DEXAMETHASONE: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL

Treatment Schema



Trial Registration clinicaltrials.gov Identifier: NCT00489307

Objectives

- To compare the effects of dexamethasone and placebo on CRF
- To determine the role of dexamethasone on anorexia, anxiety, depression, and overall symptom distress

Eligibility Criteria: Inclusion

- History of Advanced Cancer
- Fatigue ≥ 4 on the Edmonton Symptom Assessment Scale (ESAS; a 0-10 scale)
- Two other fatigue related symptoms (pain, nausea, loss of appetite, depression, anxiety, or sleep disturbance) at a score of ≥ 4/10 (ESAS)
- Normal cognition
- Hgb \ge 9g/dl
- Life expectancy 4 weeks or more

Eligibility Criteria: Exclusion

- No infections
- No history of diabetes
- No recent surgery
- Neutrophil count $\leq 750/\text{mm}^3$
- Contraindication or allergies to Dex or steroids



Patient Characteristics

Characteristics		No. of Pat	ients	
	Dexamethasone (n=67)	Placebo (n=65)	Total (n=132)	р
Age, years				
Median	60.5	60	60	0.438
Sex, n				
Male	25	37	62	0.024
Female	42	28	70	
Race, n				
White	42	39	81	0.252
Hispanic	11	10	21	
Black	13	10	23	
Asian/Other	1	6	7	
Diagnosis, n				
Breast cancer	7	6	13	0.528
Head&Neck, Lung cancer	24	21	45	
Gastrointestinal cancer	15	24	39	
Genitourinary cancer	6	4	10	
Sarcoma cancer	6	3	9	
Gynecological cancer	4	5	9	
Other	5	2	7	
FACIT-Fatigue subscale score				
Mean	18.40	21.57	19.64	0.069

PRESENTED BY: SRIRAM YENNU MD., MS

	Patient Characteris	stics		
Characteristics		No. of Pati	ents	
	Dexamethasone (n=67)	Placebo (n=65)	Total (n=132)	р
HADS – Anxiety score				
Mean	7.47	7.46	7.46	0.98
SD	4.18	3.9	4.03	
HADS – Depression score				
Mean	9.03	7.94	8.50	0.12
SD	4.22	3.23	3.80	
ESAS Physical Distress Score				
Mean	29.8	27.87	28.86	0.21
SD	8.29	8.20	8.27	
ESAS Psychological Distress Score	6			
Mean	6.43	6.64	6.53	0.84
SD	5.72	5.78	5.72	
ESAS Symptom Distress Score				
Mean	41.4	27.87	40.80	0.56
SD	13.09	8.20	13.13	

FACIT-F- Functional Assessment of Chronic Illness Therapy-Fatigue; FAACT- Functional Assessment of Anorexia/Cachexia Therapy; HADS- Hospital Anxiety Depression Scale; ESAS- Edmonton Symptom Assessment Scale

Mean improvement in the FACIT -F fatigue subscale in the dexamethasone and placebo arms



*p=0.005; **p=0.008

Results

Instrument*	Dexametha (N=43)	asone	Placebo ((N=41)		Dexametha (N=43)	sone	Placebo (N=41)	
	Day 15 - Baseline		Day 15 - Baseline			Day 8 - B	aseline	Day 8 - B	aseline	
	Mean	SD	Mean	SD	P [†]	Mean	SD	Mean	SD	Pł
FACIT Fatigue Subscale	9.0	10.30	3.1	9.59	0.008	8.01	7.81	3.06	7.28	0.005
FACIT Physical	5.25	6.01	1.32	5.52	0.002	4.37	5.14	1.34	4.50	0.007
FACIT Social/family	-0.05	5.50	0.2	4.77	0.820	-0.22	4.06	0.52	3.58	0.40
FACIT Emotional	1.85	4.93	1.18	4.49	0.490	0.59	3.57	1.44	4.07	0.33
FACIT-Functional	1.3	6.21	1.51	5.17	0.820	0.55	5.20	1.11	4.80	0.56
FACIT-F total Score	18.16	22.88	7.87	19.93	0.030	13.37	13.22	7.5	14.04	0.06

*As values were normally distributed, data are presented as means and standard deviation (SD); **I** Paired t-test; the ESAS psychological scores were not normally distributed, so Wilcoxon two-sample tests were used in those analyses. **FACIT-F** - Functional Assessment of Chronic Illness Therapy –Fatigue

Mean improvement in the ESAS Symptom Distress scores at Day 15.



*p=0.046

Results

Instrument*	Dexametha (N=43) Day 15 - Baseline	sone	Placebo (Day 15 - Baseline	N=41)		Dexametha (N=43) Day 8 - B	sone aseline	Placebo (Day 8 - B	N=41) aseline	
	Mean	SD	Mean	SD	Pt	Mean	SD	Mean	SD	P [†]
ESAS Physical	-10.15	9.8	-5.39	10.56	0.046	-7.52	8.2	-3.95	10.85	0.08
ESAS Psychological	-1.48	4.67	-2.08	4.73	0.76	-1.26	4.68	-1.81	5.01	0.91
ESAS Symptom distress	-12.2	13.49	-8.86	15.91	0.22	-10	12.28	-6.95	16.38	0.23
HADS Anxiety	-0.66	3.45	-1.00	3.54	0.75	-0.85	3.16	-1.09	2.32	0.59
HADS Depression	-1.39	3.59	-0.31	3.90	0.29	-1.23	4.02	-0.43	3.12	0.65
FAACT	15.22	19.7	6.46	19.52	0.04	9.12	14.21	5.53	16.06	0.31

*As values were normally distributed, data are presented as means and standard deviation (SD); # Paired t-test; the ESAS psychological scores were not normally distributed, so Wilcoxon twosample tests were used in those analyses. **FAACT**- Functional Assessment of Anorexia/Cachexia Therapy; **ESAS** - Edmonton Symptom Assessment Scale **HADS** – Hospital Anxiety Depression Scale.

Adverse Events

No significant difference in the number of grade ≥3 adverse events(CTC V.3.0) between dexamethasone vs. placebo group (17/62 vs. 11/58, P=0.27)

Corticosteroids (dosage and duration) in the management of cancer related symptoms

Author	Number of patients	Treatment	Study	Equivalent	Primary Outcome for the study
		Duration (days)	Drug*	Dexamethason	
				е	
				daily dose	
				(mg)	
Moertal et al. 1974 ¹⁵	116	14	DM	0.75-1.5	Cancer related symptoms
					including low appetite, strength,
					and overall survival
Wilcox et al. 1984 ²⁶	41	14	PS	2.25	Poor appetite
Bruera et al 1985 ^{43**}	40	14	MP	6	Combination of pain, tiredness,
					anorexia and depression
Della Cuna 1989 ^{14**}	40	56	МР	23	Quality of life
Popiela et al 1989 ^{13**}	173	56	MP	23	Quality of life
Loprinzi et al 1999 ^{12**}	455	30	DM	3	Low appetite
Hardy et al 2001 ²⁵	160	22	DM	12	Anorexia, nausea, low mood,
					pain and vomiting.
Mercadante et al 2001 ¹¹	376	26	DM, MP	4-16	Cancer related symptoms
					including anorexia, fatigue,
					dyspnea, neadache and
Bruera et al 200/37**	51	7	DM	20	drowsiness Chronic nausoa
	51	'		20	Chromenausea
Yennurajalingam et al 2013 ^{16**}	84	14	DM	8	fatigue
Paulsen et al 2014 ^{70**}	50	7	MP	8	pain
*MP= Methylprednisolone, DM=D	examethasone, PS=Pre	ednisolone			

** Randomized, double blind placebo controlled studies

Steroids for Symptom Distress

Potential for multiple adverse effects
Dose/time-related
Many preventable
Most reversible

Sturdza A,2008 Fardet L,2007

Steroids for Symptom Distress

- Myopathy
- Hyperglycemia
- Fluid retention
- Immunomodulation = candidiasis
- Steroid psychosis
- GI bleed, Gastritis
- Osteoporosis
- Poor wound healing

Steroids and Symptom Distress

Tissue	Effects
Liver (glucose intolerance)	Increased gluconeogenesis Increased glycogen synthesis
Skeletal Muscle (Steroid Myopathy) atrophy of type 2b muscle fibers (proximal muscles & respiratory muscles)	Decrease glucose uptake Decrease protein synthesis Increased protein degradation (activation of ubiquitin- ligase pathway); inhibition of IGF-1/insulin
Adipose	Decrease glucose uptake Increase lipid mobilization

Pereira, 2011

How to prescribe Steroids

- For short term (~ 2 weeks)
- For QOL, Fatigue, nausea and appetite
- Dexamethasone 8-16mg Orally daily most commonly used steroid
- Prednisone 40mg orally as alternative
- Long term always use Prednisone (mineralocorticoid effect)

Steroids and Relative Potency

Agent	Approx. equiv. dose (mg)	Relative anti-inflammatory (glucocortlcoid) potency	Relative mineralocorticoid (Na ⁺ retaining) potency	Biologic half-life (hrs)	
Cortisone	25	0.8	0.8	8-12	
Hydrocortisone	20	1	1	8-12	
Prednisone	5	4	0.8	18-36	
Prednisolone	5	4	0.8	18-36	
Methylprednisolone	5	5	0.5	18-36	
Dexamethasone	0.75	25	0	36-54	

http://emupdates.com/wp-content/uploads/2009/11/ICUPocketGuide.pdf-page-53-of-63.jpg

Summary

- Corticosteroids improve symptom distress("short term")
- Alleviates a number of distressing cancer related symptoms including CRF, anorexia and nausea.
- Evidence only supports its use for a maximum of days to a few weeks
- Future studies optimal dose, type & long term efficacy