1

Symptoms and their relationship to systemic inflammation in a large multinational cohort of patients with advanced cancer.

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2

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- Prof Marie Fallon (group lead –EPAS)
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3

Symptom Prevalence in Advanced Cancer

	Number of Studies	Number of Patients	Pooled Prevalence (%)	95% CI (%)
N	40	25,074		
Fatigue	17	6,727	74	(63; 83)
Pain	37	21,917	71	(67; 74)
Lack of energy	6	1,827	69	(57; 79)
Weakness	18	14,910	60	(51; 68)
Appetite loss	37	23,112	53	(48; 59)
Nervousness	5	727	48	(39; 57)
Weight loss	17	13,167	46	(34; 59)
Dry mouth	20	6,359	40	(29; 52)
Depressed mood	19	8,678	39	(33; 45)
Constipation	34	22,437	37	(33; 40)
Worrying	6	1,378	36	(21; 55)
Insomnia	28	18,597	36	(30; 43)
Dyspnea	40	24,490	35	(30; 39)
Nausea	39	24,263	31	(27; 35)

Teunissen et al, JPSM 2007

4

Are cancer pain and depression interdependent? A systematic review

Psycho-Oncology DOI: 10.1002/pon.1431
Psycho-Oncology (2008)

Barry J.A. Laird[1]*, Angela C. Boyd[1], Lesley A. Colvin[2] and Marie T. Fallon[1]

- Pain intensity, duration and certain descriptors (MPQ) associated with depression.
- Pain and depression both highly prevalent
- Certain pain features correlated with depression

5

National Institutes of Health State-of-the-Science Conference Statement: Symptom Management in Cancer: Pain, Depression, and Fatigue, July 15–17, 2002

The panel's key conclusions following its assessment of the literature are as follows:

1) Too many cancer patients with pain, depression, and fatigue receive inadequate treatment for their symptoms.
2) Clinicians should use brief assessment tools routinely to ask patients about pain, depression, and fatigue and to initiate evidence-based treatments.
3) Current evidence to support the concept of cancer symptom clusters is insufficient, and additional theoretically driven research is warranted.
4) Research is needed on the definition, occurrence, assessment, and treatment of pain, depression, and fatigue alone and in combination through adequately funded prospective studies.
5) Fear of cancer and its consequences must be ameliorated.
6) All patients with cancer should have optimal symptom control from diagnosis throughout the course of illness, regardless of personal and cultural characteristics.
7) The state of the science in cancer symptom management should be reassessed periodically.

6

Symptom Cluster

- In advanced cancer, a median of 11 symptoms (range 1-27) are present commonly (Walsh et al., 2000).
  - Symptoms can simply co-exist
  - Symptoms can co-exist and be related
  - Symptoms can co-exist and share a common pathophysiology

Symptom cluster:
" three or more concurrent symptoms that are related to each other" is the most appropriate definition (Dodd et al., 2001b).

7

Pain, depression and fatigue as a symptom cluster in advanced cancer.

Laird et al. *Journal of Pain and Symptom Management* Vol 42, No1, 2011

- n=654
- Patients with moderate under-nutrition
- EORTC QLQ-C30
- Cut-offs based on thresholds
- Multivariate and regression analyses run

8

			Trial A (n=473)		Trial B (n=181)	
Depression*	Fatigue**	Pain***	Observed Prevalence	Expected Prevalence@	Observed Prevalance	Expected Prevalence@
No	No	No	130 (27.5%)	71.2 (15.1%)	58 (32.0%)	39.0 (21.6%)
No	No	Yes	25 (5.3%)	48.7 (10.3%)	23 (12.7%)	29.6 (16.3%)
No	Yes	No	40 (8.5%)	58.7 (12.4%)	11 (6.1%)	22.4 (12.4%)
No	Yes	Yes	24 (5.1%)	40.2 (8.5%)	16 (8.8%)	17.0 (9.4%)
Yes	No	No	62 (13.1%)	82.6 (17.5%)	23 (12.7%)	26.4 (14.6%)
Yes	No	Yes	42 (8.9%)	56.5 (11.9%)	11 (6.1%)	20.0 (11.0%)
Yes	Yes	No	49 (10.4%)	68.3 (14.4%)	11 (6.1%)	15.1 (8.4%)
Yes	Yes	Yes	**101 (21.4%)**	**46.6 (9.9%)**	**28 (15.5%)**	**11.5 (6.3%)**

9

Pain, Depression, Fatigue – Symptom Cluster

- Pain, depression and fatigue exists as a specific symptom cluster in advanced cancer patients.
- Between Two and four times the number of patients with all three symptoms than would be expected. ($p<0.001$)
- Each symptom can occur in isolation and every possible pair of symptoms can occur without the third being present.
- This further supports the existence of pain, depression and fatigue as a specific symptom cluster.
- **First** study to demonstrate this cluster

10

Cytokine-Induced Sickness Behaviour

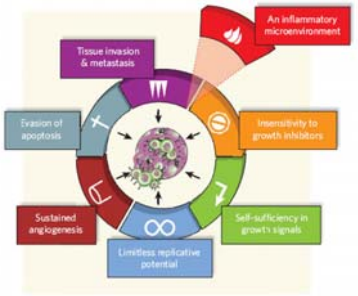
- Administration of inflammatory agents and pro-inflammatory cytokines results in "cytokine-induced sickness behaviour" (Konsman et al., 2002, Dantzer, 2004).
- Cytokine-induced sickness behaviour produces pain and behavioural changes which are comparable with pain, depression and fatigue in humans (Yirmiya, 1996, Watkins and Maier, 2000).
- In humans the response to infection, results in increased production of pro-inflammatory cytokines (IL-1, IL-6 and TNF-alpha). These pro-inflammatory cytokines correlate with clinical symptoms which mirror animal models of sickness behaviour (Vollmer-Conna et al., 2004).
- Cytokine-induced sickness behaviour resulting in pain, depression and fatigue, has been shown to exist not demonstrated in cancer.....

11

Inflammation & Cancer

- Inflammation predisposes to certain tumour types
- Inflammation implicated in oncogenic mutations & experimental animal models of tumour development [1]
- Inflammation can be a result of cancer.
- Targeting inflammation can reduce cancer risk and cancer spread.

7th hallmark of cancer



1.Mantovani Nature 2008;454

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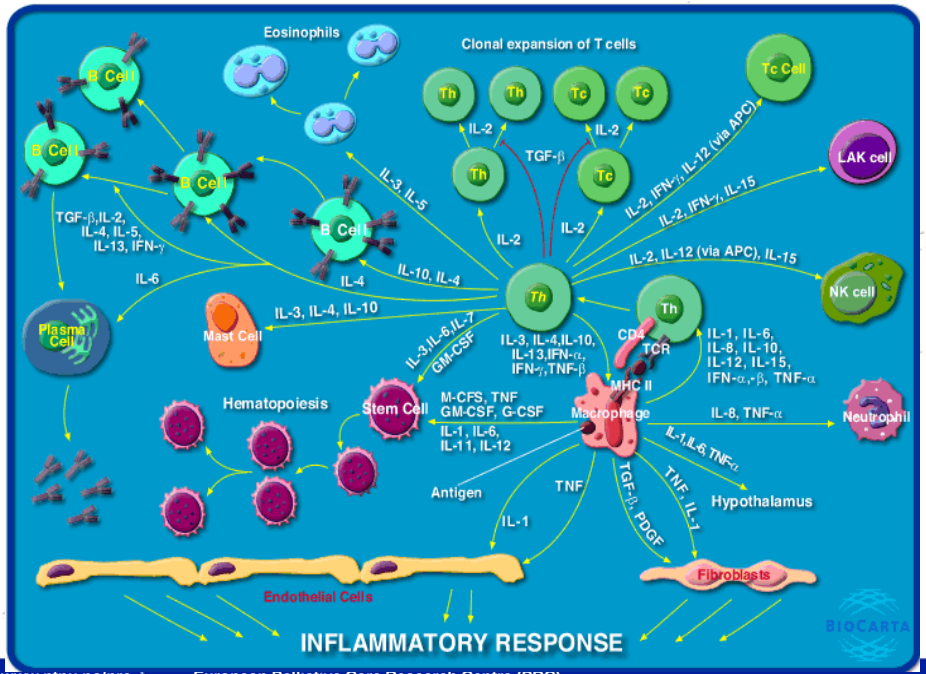
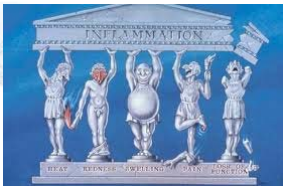


13

Measuring inflammation - CRP

- Reliable biomarker of SI in cancer
- Half-life of CRP is 19hrs
- CRP is produced under the control of interleukin-6 (IL-6).
- IL-6 pro-inflammatory cytokine and is a critical mediator of inflammation.
- IL-6 concentrations are highly correlated with CRP
- CRP serves as a biomarker for systemic inflammation ~ IL-6

14



15

PAIN® 152 (2011) 460–463

Cancer pain and its relationship to systemic inflammation: An exploratory study

Barry J.A. Laird [a,*], Angela C. Scott [a], Lesley A. Colvin [b], Amy-Louise McKeon [a], Gordon D. Murray [a], Kenneth C.H. Fearon [a], Marie T. Fallon [a]

- Aim: assess relationship between pain and systemic inflammation cohort of cancer patients;
- Secondary analysis of BH-80 and Scotia trials (JCO, Gut)
- n=449, groups well matched
- CRP used (surrogate IL-6)

16

Relationship between pain and CRP

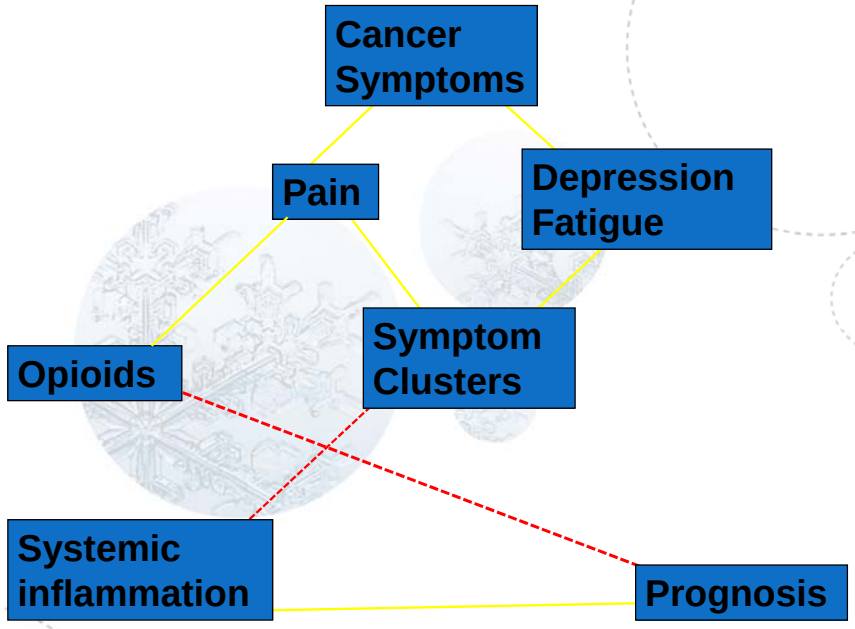
		Trial 1 N=275	Trial 2 N=174
		CRP	CRP
Pain	Pearson Correlation	0.126	0.163
Pain	Significance (2-tailed)	0.036	0.032
Pain	Number of patients	275	174

17

Pain and systemic inflammation

- Pain associated with IL-6
- Supported in basic science work (IL-6 knockout mice) (Ramer 1998)
- IL-6 admin results in allodynia and hyperalgesia (DeLeo 1996)
- Inflammatory pain – IL-6 increased
- Glial activation and IL-6 (Wieseler-Frank 2004)

18



19

Modulating the inflammatory response to treat symptoms?

20

Compound	Mechanism of action	Indication	Phase
TNFα			
Infliximab	Mouse–human chimeric TNFα-specific antibody	RA, psoriatic arthritis, psoriasis, ALS, ulcerative colitis, Crohn's disease	Approved
Adalimumab	Fully human TNFα-specific antibody	RA, psoriatic arthritis, psoriasis, ALS, juvenile RA, Crohn's disease	Approved
Golimumab	Fully human TNFα-specific antibody	RA, psoriatic arthritis, ALS	Approved
Etanercept	Fusion protein of the Fc portion of a human antibody and the ligand-binding portion of the human TNF receptor	RA, psoriatic arthritis, psoriasis, ALS, juvenile RA	Approved
Certolizumab	PEG-conjugated, humanized, antigen-binding fragment (F(ab')) of a TNFα-specific antibody	RA, Crohn's disease	Approved
ANO128	Small-molecule TNFα inhibitor	Acne Pyelonephritis	I II
ART621	TNFα-specific domain antibody comprising the smallest antigen-binding unit of the antibody	RA, psoriasis, sciatica	II
TNFα nanobody	TNFα-specific nanobody, antibody-derived therapeutic proteins that contain the unique structural and functional properties of naturally occurring heavy-chain antibodies	RA	I
IL-6			
Tocilizumab	Humanized IL-6 receptor-specific mAb	RA, juvenile RA, Crohn's disease, Castleman's disease	Approved
CNTO 136	Fully human IL-6-specific mAb	RA	II
CNTO 328	Chimeric IL-6-specific mAb	Multiple myeloma, prostate cancer	II
ALD518	Humanized IL-6-specific mAb	RA	II
C326	Novel avimer protein therapeutic, smaller than most therapeutic proteins and antibodies	Crohn's disease	I
CDP6038	IL-6-specific mAb	Autoimmune disorders	I
REGN88	Fully human mAb to the IL-6 receptor	RA	I
CRS/18	Soluble gp130–Fc fusion protein	Inflammation	Preclinical
IL-1			
Anakinra	Recombinant nonglycosylated human IL-1 receptor antagonist	RA	Approved
Canakinumab	Human IL-1β-specific mAb	Gout, juvenile RA, COPD Cryopyrin-associated periodic syndrome	II Approved
XOMA 052	Human IL-1β-specific mAb	RA, type 2 diabetes	II
Rilonacept (also called IL-1 Trap)	Dimeric fusion protein of the ligand-binding domains of IL-1 receptor type I and IL-1 receptor accessory protein fused to human IgG1	Cryopyrin-associated periodic syndrome Gout Coronary atherosclerosis RA, anaemia	Approved III II I
CYT013-IL1bOb	Vaccine	Type 2 diabetes	I/II
IL-23			
Ustekinumab	Fully human IL-12/23-specific mAb targeting the p40 subunit	Psoriasis Psoriatic arthritis, Crohn's disease	Approved II
ABT874	Fully human IL-12/23-specific mAb targeting the p40 subunit	Psoriasis, Crohn's disease	III, II
Apilimod	Orally administered, small molecule inhibits the production of IL-12 and IL-23	RA, Crohn's disease	II
IFNγ			
AMG 811	Fully human IFNγ-specific mAb	SLE	I
IL-17			
AIN457	Fully human IL-17A-specific mAb	RA, Crohn's disease, psoriasis, psoriatic arthritis Uveitis	II III
LY2439821	Humanized IL-17-specific mAb	RA	II
AMG 827	Fully human IL-17 receptor-specific mAb	RA, psoriasis	II
RG4934	IL-17-specific mAb	Psoriatic arthritis	I
IL-22			
Fezakinumab	IL-22-specific mAb	RA Psoriasis	II I
IL-4 and IL-13			
AMG317	IL-4 receptor-α-specific mAb (inhibits IL-4 and IL-13 signalling)	Asthma	II
Pitrakinra	Recombinant human IL-4 variant that is an inhibitor of IL-4 and IL-13 receptors	Asthma	II
Nuvance	Genetically engineered soluble human IL-4 receptor (inhibits IL-4 and IL-13 signalling)	Asthma	II
AIR645	2′-O-methoxyethyl antisense drug targeting the IL-4 receptor-α mRNA	Asthma	I
IL-13			
Anrukinzumab	Humanized IL-13-specific mAb	Asthma	II
Lebrikizumab	Humanized IL-13-specific mAb	Asthma	II
CAT-354	Fully human IL-13-specific mAb	Asthma	II
IMA-026	IL-13-specific mAb	Asthma	II
IL-5			
Mepolizumab	Humanized IL-5-specific mAb	Hypereosinophilic syndrome Asthma, eosophagitis	III II
MEDI-563	Humanized IL-5-specific receptor mAb	Asthma	II
Reslizumab	Humanized IL-5-specific mAb	Eosophagitis Asthma	III II

ALS, amyotrophic lateral sclerosis; COPD, chronic obstructive pulmonary disease; Fc, crystallizable fragment; GM-CSF, granulocyte–macrophage colony-stimulating factor; Ig, immunoglobulin; IL, interleukin; mAb, monoclonal antibody; PEG, polyethylene glycol; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TNF, tumour necrosis factor.

21

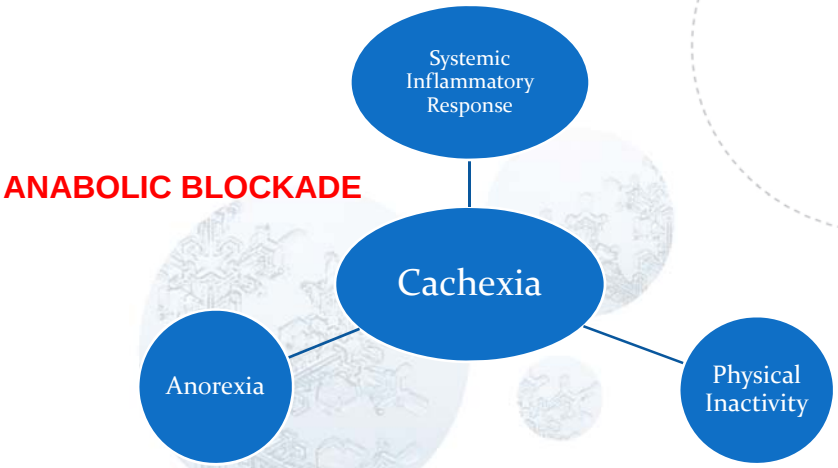
- Symptoms linked
- Symptoms related to inflammation
- Inflammation related to prognosis

- Are symptoms related to prognosis?

22

World Health Organization definition of palliative care: an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the **prevention** and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychological and spiritual

23



Interventions should be multimodal tackling all of these issues simultaneously

24

preMENAC Study

A multicentre, open, randomized phase II study comparing a multimodal intervention (oral nutritional supplements, celecoxib and physical exercise) for cachexia versus standard cancer care.
(EudraCT number: 2010-022897-14)

Modulating the inflammatory response on a background of optimal symptom control.

EAPC

PRC European Palliative Care Research Centre

Thank you.

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