Cytokines, Fatigue, and Cutaneous Erythema in Early Stage Breast Cancer Patients Receiving Adjuvant Radiation Therapy

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Background

Breast cancer patients receiving adjuvant therapy:
cancer-related fatigue prevalence 25-99%*

Biological mechanisms underlying fatigue during RT

?

*Andrykowski MA et al, J Clin Oncol 2005

Background

Breast cancer patients

Increase of fatigue during adjuvant RT (40 pts)
no association with anxiety/depression
and/or cytokines levels (TNF-α, IL-1β, and IL-6)

No significant association between
fatigue and biological disorders in 302 pts with
breast cancer receiving adjuvant RT
and/or chemotherapy

No consensus !

Significant correlation between fatigue
and high levels of pro-inflammatory markers
(IL-1ra,IL-6, and sTNT-RII)

Geinitz et al. Int J Radiat Oncol Biol Phys 2005
Noal et al. Int J Radiat Oncol Biol Phys 2011

Bower JE, Psychosomatic Medicine 2002
Collado-Hidalgo A Clin Cancer Research 2006

End-points

Prospective study – 40 patients (early-stage breast cancer)

Preliminary investigation, patients with homogeneous characteristics

Primary hypothesis : high-grade erythema of the breast skin during RT

high levels of serum pro-inflammatory cytokines

fatigue symptoms

Secondary end-point: assess other factors (hormonal therapy, breast volume, anemia) that may influence cytokine-related biological mechanisms leading to fatigue

Materials and Methods

Table 1: Patients' characteristics (n = 40).

	Number of patients (% of total)
Mean age (years) 55	
Range (years) 40–73	
T, stage	
Tis	19 (48)
T1	21 (52)
N, stage	
N0	40 (100)
Histological type	
DCIS	16 (40)
Ductal	17 (43)
Lobular	2 (5)
Others	5 (12)
Tumor grade (G)	
Poorly differentiated (G3)	10 (25)
Moderately differentiated (G2)	13 (32)
Well differentiated (G1)	17 (43)
Radiotherapy schedule	
50 Gy/2 Gy	19 (48)
50 Gy/2 Gy + Boost 10 Gy/2.5 Gy	21 (52)

Inclusion criteria

- age ≤ 75 years
- conserving surgery
- early stage disease
- no nodal involvement
- standard post-operative radiotherapy
- no previous chemotherapy
- lack of significant co-morbid conditions

Highly selected population

Materials and Methods

Treatment – adjuvant EBRT: breast + boost (Stage I pts) 6MV linear accelerator
RT schedule: total dose of 50Gy/25 fr - 5 days per week.
Boost to the tumor bed: total dose of 10Gy/4 fr delivered with a direct electron field

The breast volume in cubic centimeters (cc) was measured for each patient
Large breast : volume ≥ 1000 cc

Hormonal therapy was administered to all stage I patients.

Skin Erythema – graded according to RTOG scale
High grade: grade ≥ 2

Materials and Methods

Diagnosis of cancer-related fatigue according to the criteria described by Cella et al.

1. Significant fatigue experienced each day in at least two weeks within the preceding month
2. Significant distress or impairment of functioning due to fatigue symptoms
3. Clinical evidence of fatigue as a consequence of cancer or **cancer therapy**
4. No concurrent diagnosis of psychiatric disorders (i.e major depressive disorders)

Questionnaires – Anxiety/depression : baseline, weekly, 3 months, 6 months

HADS (Hospital Anxiety and Depression Scale)

Total score range: 0 – 21

Significant clinical levels of anxiety/depression: total score ≥ 11

Zigmond AS, et al. Acta Psychiatr Scand 1983

Materials and Methods

Questionnaires – Fatigue: baseline, weekly, 3 months, 6 months

Fatigue – FACT-F (Functional Assessment of Cancer Therapy Fatigue) subscale - component of FACT-G quality of life questionnaire

13 items (0-5 points for each item) - total score (range: 0-52) – fatigue severity

Presence of fatigue : final score < 37

fatigue symptoms - score < 37 for two consecutive weeks

no associated depression/anxiety

Cella et al. J Clin Oncol 1993, Cella et al. Oncology 1997

Materials and Methods

Cytokines

Blood samples: baseline, weekly during treatment, at 3 months, and at 6 months from RT completion

12 inflammatory cytokines were tested

IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, VEGF, EGF, TNF-α, IFN-γ, MCP-1

Simultaneous and serial assessment of plasmatic cytokines: multiplex biochip array in Evidence Investigator equipment (Randox Labs. Ltd. Crumlin, UK)

Control group: 10 healthy volunteers (35-66 years old) to define the cut-off value for each cytokine

Materials and Methods

Statistical analysis

Heckman two-step equation: heterogeneity between patients

other factors that can increase cytokines level (non explain by skin erythema)

1. Markers$*$ it = β0 + β1Erythemait + bi + εit,
   Markersit = 1 ←→Markers$*$ it > 0,
   $bi \sim N(0, \sigma 2b)$

2. Fatigue$*$ it = γ0 + γ1Breast Volume i + γ2HormoneTherapyit + γ3Markersit + $\gamma 4Mit$ + ui + eit,
   Fatigueit = 1 ←→Fatigue$*it$ > 0,
   $ui \sim N(0, \sigma 2u)$

Results

Fatigue - anxiety/depression - erythema

17 (42.5%) patients - fatigue symptoms during RT and follow-up

12 (30%) patients - depression/anxiety at baseline /during treatment

10 patients – fatigue

7 (17.5%) patients – fatigue symptoms not associated to depression/anxiety

Grade ≥ 2 erythema in 5/7 patients with fatigue symptoms

Grade ≥ 2 erythema in 16/40 (38%) patients

Results

Cytokines

6/12 cytokines: significant differences between healthy donors and pretreated breast cancer patients

IL-1β, IL-2, IL-6, TNF-α, IL-8, and MCP-1: altered in breast cancer patients

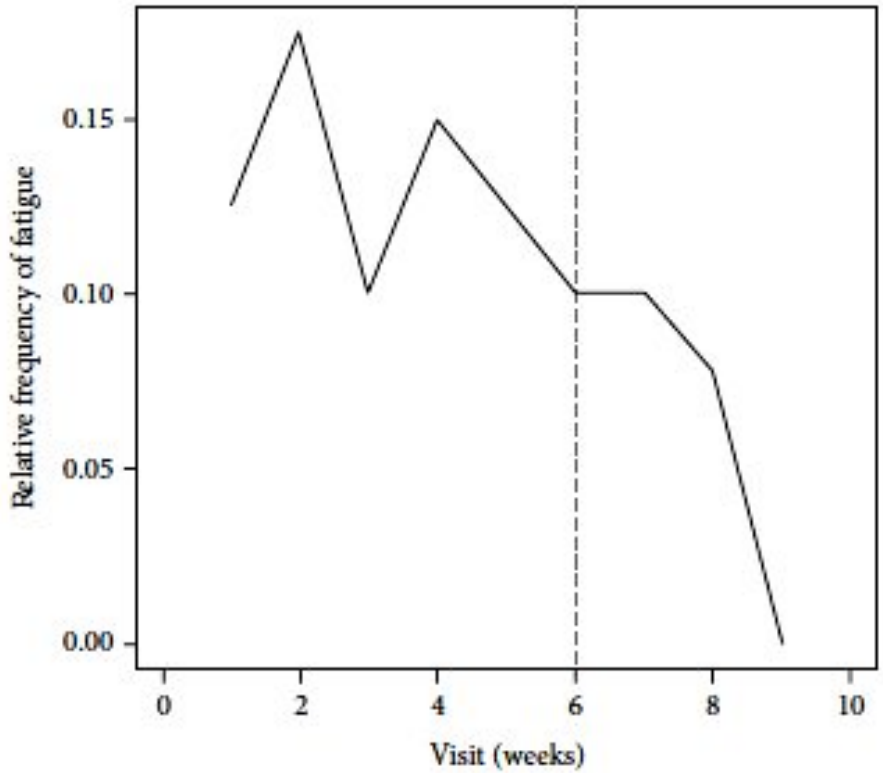
IL-1β, IL-2, IL-6, and TNF-α : significantly increased 4 weeks after RT ($P < 0.05$, compared to pretreated samples)

	Mean values of cytokines (pg/mL)					
	IL-1β	IL-2	IL-6	IL-8	MCP-1	TNF-α
HD	*0.106*	*2.103*	*0.921*	*3.241*	*350.54*	*0.948*
Patients pre-RT	1.9	3.05	2.65	5.309	245.52	1.41
Patients 4 weeks after RT	4.27	4.84	12.95	19.03	480.38	4.84
Patients 6 months after RT	3.49	3.58	6.34	7.83	379.97	3.58
t-test (HD versus pre-RT)	$5.42e-17^{*}$	*0.00278**	$2.44e-09^{*}$	*0.42687*	*0.04959**	$7.702e-05^{*}$
t-test (pre-RT versus 4 w)	0.02682*	0.00016*	0.04853*	0.05191	0.06744	0.00165*
t-test (pre-RT versus 6 m)	0.09564	0.0673	0.3087	0.05585	0.24408	0.00826*

$^{*}P < 0.05$.

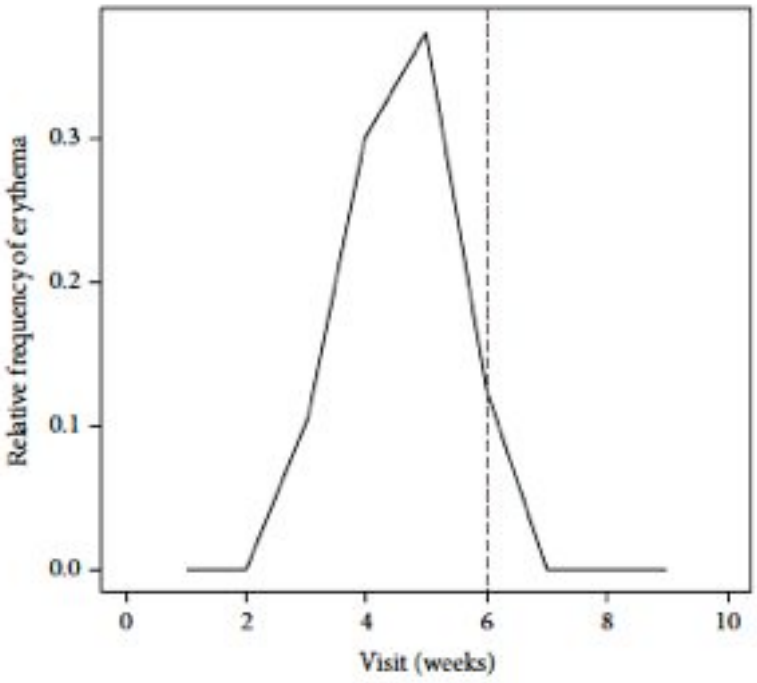
Results

Fatigue over time

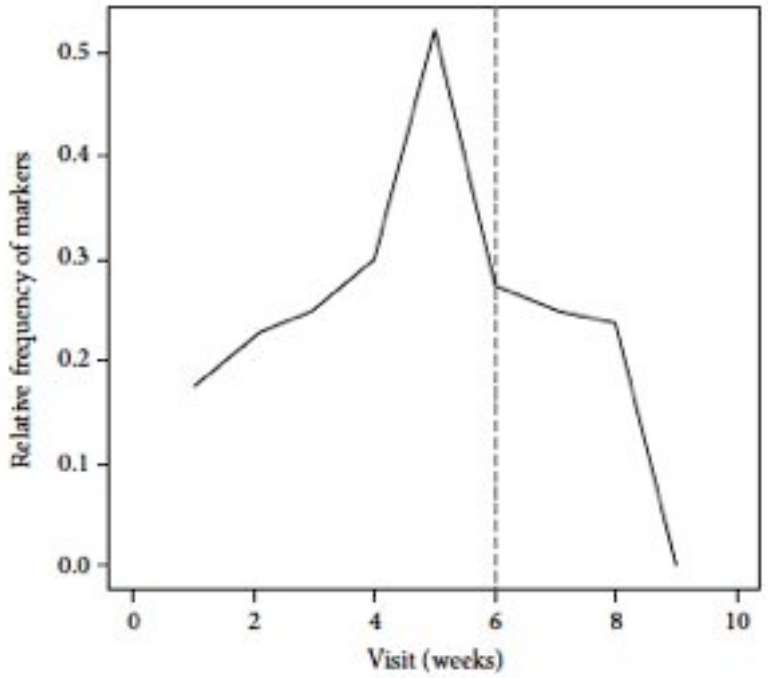


Results

Erythema



Cytokines



Results

Erythema ⟷ ***Pro-inflammatory Cytokines***

Step 1 of Heckman equation

Erythema significantly influenced the increase in pro-inflammatory cytokines levels: IL-1β, IL-2, IL-6 and TNF-α (p=0.00001)

Variable	Coefficient	Standard Error	P value
Probit model for the inflammatory markers			
Intercept	−1.648	0.352	$2.87e-06$
Erythema	2.065	0.468	$1.01e-05$
σ^2_b	3.792		

Results

Fatigue ⟷ ***Pro-inflammatory Cytokines***

Step 2 of Heckman equation

Fatigue symptoms were significantly influenced by increased blood levels of pro-inflammatory cytokines

Variable	Coefficient	Standard Error	*P* value
	Probit model for the fatigue		
Intercept	−8.574	3.460	0.0132
Breast volume	0.004	0.003	NS
Inflammatory markers	3.075	1.381	0.0260
Hormone therapy	1.975	1.923	NS
Mi	1.967	0.875	0.0246
σ^2_u	6.722		

NS: not significant.

Conclusions

Fatigue symptoms ⟷ Pro-inflammatory cytokines (increase during RT)
⟷ Concurrent high-grade breast skin erythema

High-grade breast skin erythema during RT might be responsible for biological mechanisms of fatigue, activating serum pro-inflammatory cytokine

Potential modulation of radiation therapy or new drugs erythema-targeted can be developed to reduce skin erythema intensity and fatigue, increasing adherence to therapy and quality of life

Conclusions

Next step

Study long-term fatigue

Associazione Italiana Radioterapia Oncologica

GRAZIE