Stimuler appétit

Patrick Ritz

CHU de Toulouse

La cachexie du cancer est une maladie multi-systémique

1. Increased glucose, lipid, and protein needs;
2. Inadequate food intake due to anorexia, nausea, and vomiting;
3. Stimulation of gluconeogenesis, glycogenolysis and ketogenesis from amino acids and fatty acids as sources of metabolic fuel with consequent depletion of protein and lipid stores and subsequent weight loss;
4. Peripheral resistance to insulin with impaired use of glucose;
5. Oxidative damage induced by ROS on DNA, membrane lipoproteins, and enzymes and co-enzymes that play a major role in the regulation of the main cell catabolic pathways.

1) Les corticoïdes, l'acétate de mégestrol et l'acétate de médroxyprogestérone sont des médicaments orexigènes
2) Ils peuvent être proposés, tout en tenant compte des effets indésirables potentiels, pour atténuer l'anorexie et la perte de poids des patients atteints de cancer, essentiellement en situation palliative
3) Leurs modalités optimales d'utilisation ne sont pas connues et doivent faire l'objet d'évaluation dans le cadre d'essais thérapeutiques
4) En l'absence de données objectives, la cyproheptadine*, le métoclopramide, la nandrolone et la pentoxifylline ne doivent pas être utilisés en dehors d'essais thérapeutiques prospectifs
5) Le sulfate d'hydrazine ne doit pas être utilisé.

* Sauf peut-être carcinoïdes (Behl D et al 2007)

Desport JC et al, SOR, Bull Cancer 2000, 87: 315-28

Règles utilisation

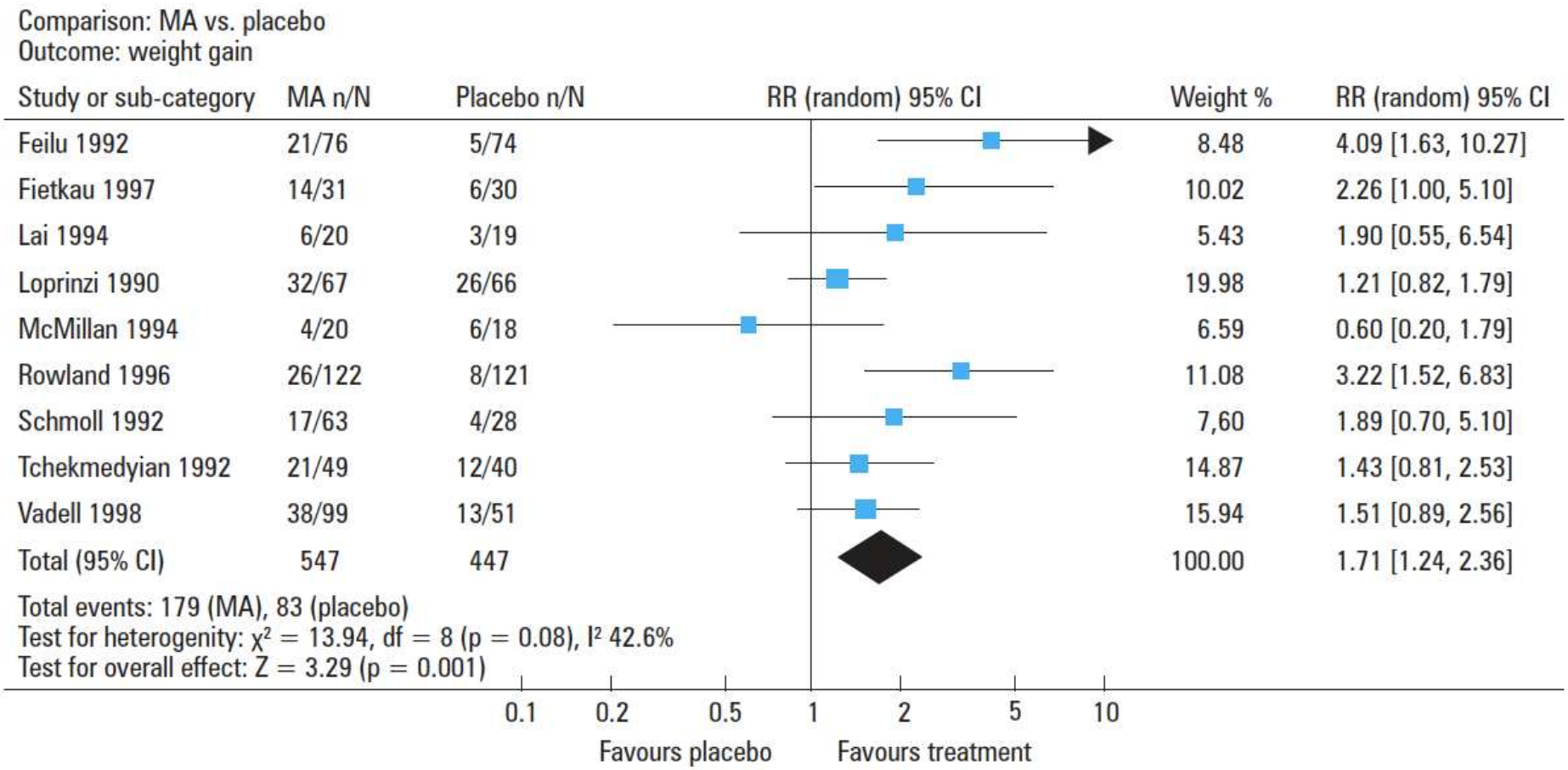
- Le meilleur stimulant de l'appétit est le traitement de la tumeur
- Traiter d'abord les autres causes de perte d'appétit
  - Mycoses buccales
  - Obstructions
  - Nausées
  - Douleur
  - Dépression
- Ce sont des palliatifs avec des effets secondaires

Behl D et al Expert Opin Pharmacother, 2007;8:1085-10

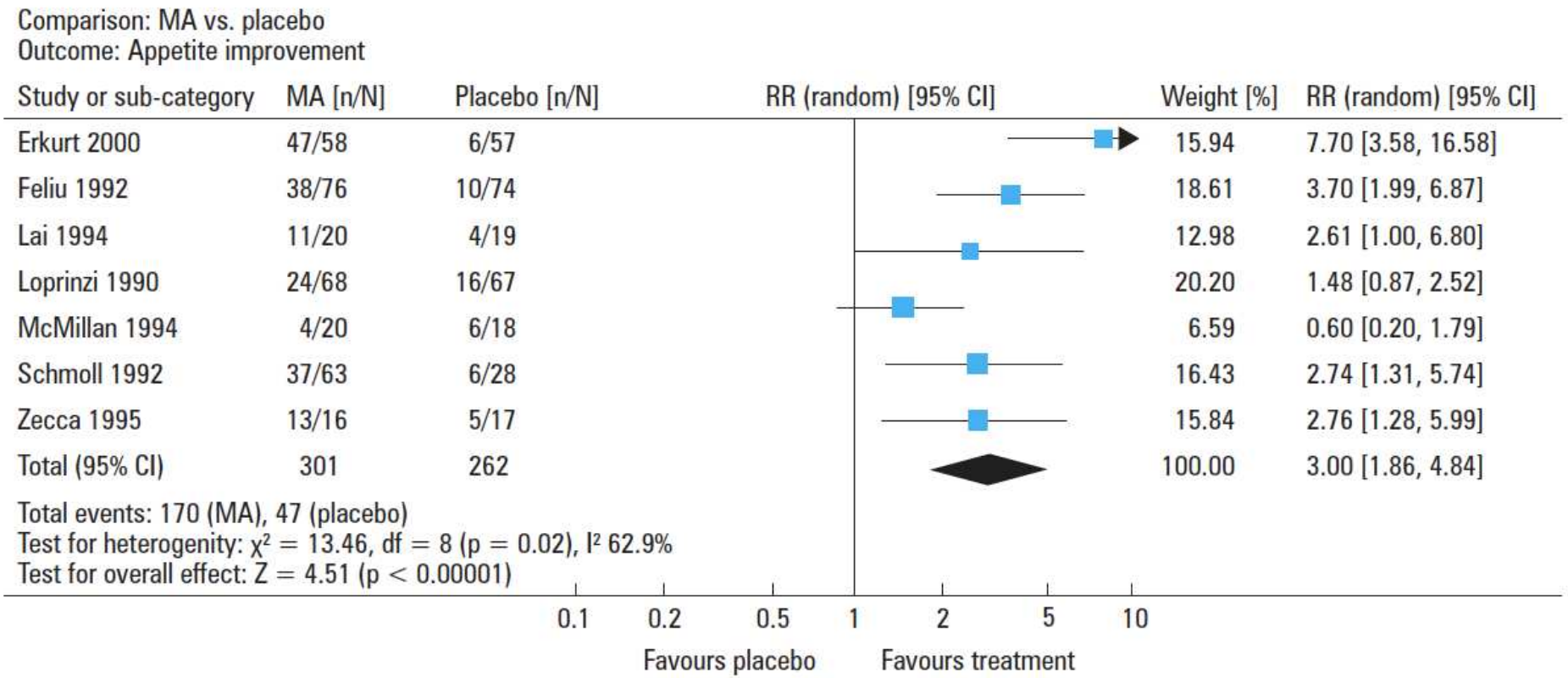
Berenstein EG, Ortiz Z. Megestrol acetate for the treatment of anorexia–cachexia syndrome. Cochrane Database Syst Rev 2005(2):CD004310

- 30 études, 4123 patients
- Doses 480-800 mg, plateau à 800 mg
- Efficacité à partir de 160 mg/j (1cp)
- Prise de masse grasse et d'eau, pas de masse maigre
- QOL

Behl D et al Expert Opin Pharmacother, 2007;8:1085-10



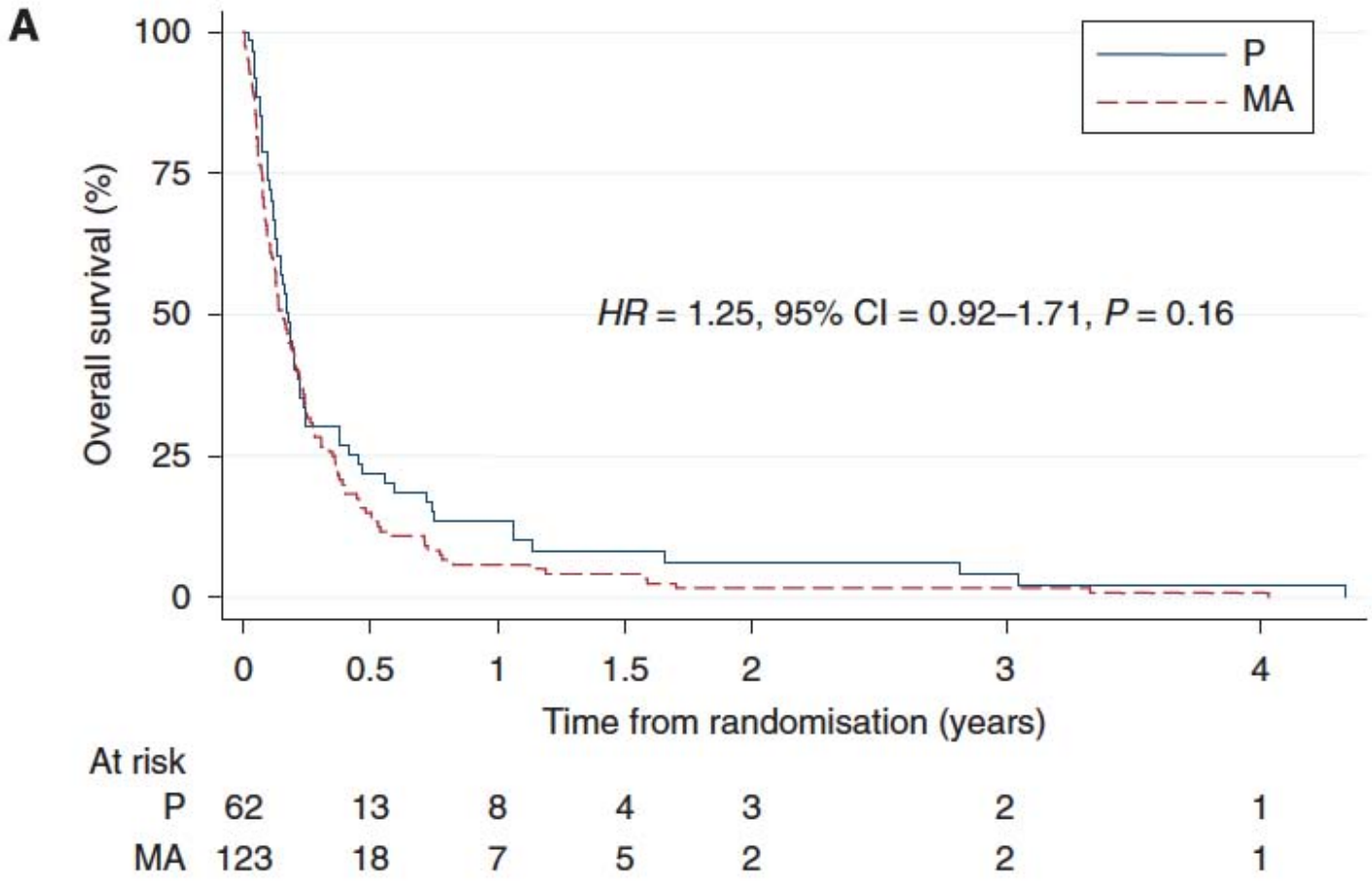
Lesniak et al Pol Arch Med Wewn 2008; 118:636-44



Lesniak et al Pol Arch Med Wewn 2008; 118:636-44

Hepatocellular carcinoma: megestrol acetate *vs* placebo

PKH Chow *et al*



Chow PKH et al, British Journal of Cancer (2011) 105, 945 – 952

MA: effets secondaires

- Ceux des progestatifs
- Impuissance
- Ménorragies
- Complications thromboemboliques
- Insuffisance surrénale

Behl D et al Expert Opin Pharmacother, 2007;8:1085-10

Glucocorticoides

- Dexaméthasone : 2-4 mg
- Methyl-prednisolone : 32 mg
- Efficacité à court terme
- Effets secondaires: estomac, os, muscle, insuffisance surrénalienne

Behl D et al Expert Opin Pharmacother, 2007;8:1085-10

Autres traitements: mythes

- THC
  - Peu d'effet vs. placebo
  - Effet très inférieur au MA
- Acides gras oméga 3
  - 4 études de phase 3, plus de 1000 patients, aucun effet

Behl D et al Expert Opin Pharmacother, 2007;8:1085-10

- La combinaison de MA avec dronabinol ou oméga-3 ne fait pas mieux en terme de prise alimentaire ou de prise de poids que le MA seul
- essai de phase 3 avec d'autres combinaison, active sur appétit, métabolisme, inflammation

Maddedu C et al Clinical Nutrition 31 (2012) 176-182

Gynecologic Oncology 124 (2012) 417–425

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

A randomized phase III clinical trial of a combined treatment for cachexia in patients with gynecological cancers: Evaluating the impact on metabolic and inflammatory profiles and quality of life

Antonio Macciò [a,*], Clelia Madeddu [b], Giulia Gramignano [c], Carlo Mulas [a], Carlo Floris [d], Eleonora Sanna [d], Maria Chiara Cau [b], Filomena Panzone [b], Giovanni Mantovani [b]

[a] *Department of Obstetrics and Gynecology, Sirai Hospital, Carbonia, Italy*
[b] *Department of Medical Oncology, University of Cagliari, Cagliari, Italy*
[c] *Medical Oncology Unit, "N.S. Bonaria" Hospital, San Gavino, Italy*
[d] *Medical Oncology Unit, Nuova Casa di Cura, Decimomannu, Cagliari, Italy*

Bras 1 : MA plus L-carnitine, celecoxib, and antioxidants (ac lipoique et carbocystéine)
Bras 2 : MA seul (320 mg/j)

	Arm 1 No. (%)	Arm 2 No. (%)	p[a]
Patients enrolled	72	72	
Patients evaluable	61	63	
Age (years)	62.6 ± 12.3	58.44 ± 13.3	n.s.
Weight (kg)	52.0 ± 9.4	50.7 ± 8.2	n.s.
Height (cm)	154.8 ± 9.1	156 ± 5.9	n.s.
BMI			
<18.5	12	14	n.s.
18.5–25	48	48	
>25	1	1	
Weight loss			
<5	1	1	n.s.
5–10%	35	34	
>10%	25	28	
Tumor site			
Ovary	24	26	n.s.
Endometrium	25	24	
Cervix	12	13	
Stage of disease			
IIIC (ovary)	2	3	n.s.
IV	59	60	

Maccio A et al. Gynecologic Oncology 124 (2012) 417–425

ECOG PS			
0	2	3	n.s.
1	17	16	
2	32	33	
3	10	11	
Glasgow Prognostic Score			
0	8	6	n.s.
1: albumin<32 g/l	6	8	
1: CRP>10 mg/l	25	26	
2	22	23	
Concomitant palliative chemotherapy			
Yes	43	47	n.s.
No	18	16	

Maccio A et al. Gynecologic Oncology 124 (2012) 417–425

Parameter	Arm 1			Arm 2			Comparison
	Baseline	After treatment	p[a]	Baseline	After treatment	p[a]	p[b]
Primary endpoints							
LBM (kg) DEXA	43 ± 10.9	45.4 ± 10.2	**0.002**	44.4 ± 7.6	45.7 ± 8.2	0.584	**0.032**
REE (kcal/day)	1166 ± 440	1042 ± 303	**0.037**	1156.6 ± 279	1312 ± 198	0.355	**0.046**
Fatigue (MFSI-SF score)	26.3 ± 17.1	19.9 ± 20.5	**0.045**	22.6 ± 15.9	23.5 ± 18.2	0.483	**0.049**
EORTC-QLQ C30	53.8 ± 17.4	61.3 ± 20.9	**0.029**	57 ± 12.8	61.1 ± 15.5	0.266	**0.042**

Maccio A et al. Gynecologic Oncology 124 (2012) 417–425

Parameter	Arm 1			Arm 2			Comparison
	Baseline	After treatment	p[a]	Baseline	After treatment	p[a]	p[b]
Secondary endpoints							
Grip strength (kg)	24.2 ± 7.2	27.2 ± 13.9	0.399	25.4 ± 8.1	24.3 ± 8.9	0.140	0.302
Appetite	4.5 ± 2.1	6 ± 1	**0.019**	5.1 ± 1.6	6.3 ± 1.5	**0.040**	0.774
ECOG PS	1.75 ± 0.5	1.12 ± 0.8	**0.001**	1.6 ± 1	1.1 ± 1.16	**0.035**	0.231
GPS	1.3 ± 0.77	0.9 ± 0.8	**0.003**	1.3 ± 0.8	1.2 ± 0.8	0.056	0.241
IL-6 (pg/ml)	22.3 ± 11.3	12.9 ± 10.5	**0.05**	27.2 ± 20	28.2 ± 23.8	0.622	**0.003**
TNF α (pg/ml)	43.4 ± 20.6	21.4 ± 22.6	**0.036**	41 ± 23.3	54 ± 25.3	0.829	**0.04**
CRP (mg/l)	24.5 ± 7.6	15.3 ± 6.7	**0.038**	28.6 ± 15.2	21.2 ± 19.7	0.292	0.056
Leptin (ng/ml)	7.9 ± 6.2	18 ± 10.8	**0.034**	6.5 ± 4.6	12 ± 10.7	0.369	**0.048**
ROS (FORT U)	528 ± 103	444 ± 71.9	**0.006**	460 ± 132	427 ± 102	0.092	**0.037**
GPx (U/l)	6007 ± 1859	7458 ± 3554	0.233	6621 ± 3417	7304 ± 5521	0.320	0.185
SOD	85 ± 14	96 ± 12	0.185	91 ± 17	94 ± 15	0.231	0.345

Maccio A et al. Gynecologic Oncology 124 (2012) 417–425

Secondary endpoints							
Grip strength (kg)	24.2 ± 7.2	27.2 ± 13.9	0.399	25.4 ± 8.1	24.3 ± 8.9	0.140	0.302
Appetite	4.5 ± 2.1	6 ± 1	**0.019**	5.1 ± 1.6	6.3 ± 1.5	**0.040**	0.774
ECOG PS	1.75 ± 0.5	1.12 ± 0.8	**0.001**	1.6 ± 1	1.1 ± 1.16	**0.035**	0.231
GPS	1.3 ± 0.77	0.9 ± 0.8	**0.003**	1.3 ± 0.8	1.2 ± 0.8	0.056	0.241
IL-6 (pg/ml)	22.3 ± 11.3	12.9 ± 10.5	**0.05**	27.2 ± 20	28.2 ± 23.8	0.622	**0.003**
TNF α (pg/ml)	43.4 ± 20.6	21.4 ± 22.6	**0.036**	41 ± 23.3	54 ± 25.3	0.829	**0.04**
CRP (mg/l)	24.5 ± 7.6	15.3 ± 6.7	**0.038**	28.6 ± 15.2	21.2 ± 19.7	0.292	0.056
Leptin (ng/ml)	7.9 ± 6.2	18 ± 10.8	**0.034**	6.5 ± 4.6	12 ± 10.7	0.369	**0.048**
ROS (FORT U)	528 ± 103	444 ± 71.9	**0.006**	460 ± 132	427 ± 102	0.092	**0.037**
GPx (U/l)	6007 ± 1859	7458 ± 3554	0.233	6621 ± 3417	7304 ± 5521	0.320	0.185
SOD	85 ± 14	96 ± 12	0.185	91 ± 17	94 ± 15	0.231	0.345

Maccio A et al. Gynecologic Oncology 124 (2012) 417–425

- RCT n=332
  - MA (320 mg) ou medroxyprogestérone (500 mg)
  - EPA
  - L-carnitine (4g)
  - Thalidomide (200 mg/j)
  - La combinaison des 4

- La combinaison améliore de façon significative la masse maigre, la dépense musculaire et la fatigue

Maddedu C et al Clinical Nutrition 31 (2012) 176-182

- RCT n=31 par groupe
  - Celecoxib (inh cox2) et L-carnitine (4g)
  - Celecoxib (inh cox2) et L-carnitine (4g) plus MA (320 mg)
- Alimentation apportant polyphenols, ac lipoique, carbocystéine, vit A, E, C dans les deux bras
- Critère pal de jugement: masse maigre et activité physique

Mantovani G et al Oncologist 2010;15:200-11

Primary and secondary endpoints before and after treatment.

Parameter	Arm 1			Arm 2			Comparison between arms
	Baseline	After treatment	p^a	Baseline	After treatment	p^a	p^b
Primary endpoints							
LBM (kg)							
BIA	39.8 ± 8.3	40.9 ± 8.7	0.316	41.0 ± 57.5	44.6 ± 5.9	0.676	0.407
DEXA	38.6 ± 9.5	41.0 ± 9.2	**0.026**	41.3 ± 7.5	43.8 ± 6.4	**0.036**	0.333
L3-TC	31.9 ± 12.6	32.4 ± 10.9	**0.048**	40.5 ± 6	41.8 ± 8.5	**0.041**	0.656
Physical activity							
Steps (count)	2739 ± 2595	3129 ± 2256	0.677	1803 ± 1209	3131 ± 2958	*0.061*	0.086

Mantovani G et al Oncologist 2010;15:200-11

Primary and secondary endpoints before and after treatment.

Parameter	Arm 1			Arm 2			Comparison between arms
	Baseline	After treatment	p^a	Baseline	After treatment	p^a	p^b
Secondary endpoints							
Grip Strength (Kg)	26.1 ± 8.9	29.9 ± 7.8	0.140	27.5 ± 8.2	29.2 ± 9.1	0.380	0.338
6MW (meters)	429 ± 55.8	474 ± 78.5	**0.015**	411 ± 86.6	464 ± 96.5	**0.038**	0.626
REE (Kcal/day)	1334.6 ± 279.9	1245 ± 429	**0.041**	1440.6 ± 139.8	1321 ± 213	**0.048**	0.448
Fatigue (MFSI-SF score)	27.3 ± 19.1	19.9 ± 16.6	**0.036**	22.3 ± 21.8	13.5 ± 11.8	**0.025**	0.981
Body weight (kg)	54.6 ± 12.6	55.4 ± 11.8	0.455	54.7 ± 10.8	57.2 ± 11.8	**0.053**	0.342
Appetite (score)	6.2 ± 2.3	7.6 ± 2.8	**0.046**	5.9 ± 1.8	7.3 ± 2.3	**0.016**	0.250
IL-6 (pg/ml)	24.7 ± 28.2	20.6 ± 17.8	0.543	22.4 ± 26.8	19.4 ± 29.2	0.781	0.877
TNF alpha (pg/ml)	27 ± 4.96	26.4 ± 5.2	0.829	27.6 ± 9.4	26.5 ± 6.7	0.475	0.548
CRP (mg/l)	29 ± 37.3	21.2 ± 19.7	0.291	21.8 ± 28.1	10.3 ± 11.6	0.239	0.840
ECOG PS	1.8 ± 0.5	1.4 ± 0.7	**0.009**	1.7 ± 0.6	1.4 ± 0.8	**0.030**	0.796
GPS Score	1.2 ± 0.7	0.8 ± 0.6	**0.003**	1.1 ± 0.7	0.6 ± 0.6	**0.015**	0.698
EORTC-QLQ-C30	60.6 ± 16.3	61.9 ± 16.6	0.333	63.9 ± 16.2	70.5 ± 16.2	0.258	0.514

Mantovani G et al Oncologist 2010;15:200-11

STUDY	DESIGN	RESULTS
CANCER		
Loprinzi 1990 (142)	RBPPS, megestrol dose 800 mg/d, 133 patients, vairous advanced cancers, therapy duration 4 months.	Improved appetite, intake, weight. Less nausea & emesis compared with placebo. Improved quality of life. Side Effects: edema (more with megestrol than with placebo).
Tchekmedyian 92 (143)	RBPPS, megestrol dose 1600 mg/d, various advanced cancers, 89 patients, therapy duration 6 weeks to 6 months.	Increased appetite, food intake, greater change in prealbumin. No change in anthropometrics – except weight. No differences in quality of life. Positive response with crossover design. Side Effects: edema.
Feliu 92 (144)	RBPPS, megestrol dose 240 mg/d, various advanced cancers, 150 patients, therapy duration 2 months.	Weight gain, increased appetite score, fewer patients with decreased performance status compared with placebo. Side Effects: Edema (no different than placebo). Improved quality of life.
Fietkau 97 (145)	RBPPS, megestrol dose 160 mg/d, head/neck cancers on radio-therapy, 61 patients.	Maintained weight and nutritional parameters during chemo-/radio-therapy in megestrol group, compared with parameter deterioration in placebo; improved quality of life with megestrol. Side Effects: none.
AIDS		
von Roenn 94 (146)	RBPPS, therapy duration 3 months, 270 patients, megestrol dose 100/400/800 mg/d.	Increased body weight and quality of life.
Oster 94 (147)	RBPPS, therapy duration 3 months, 100 partients, megestrol dose 800 mg/d.	Increased body weight and quality of life.

Karcic E et al J Nutr Health Aging 2002; 6: 1-8

Table 1. Effective or promising agents.

Partially effective agents	Progestational agents
	Corticosteroids
Promising agents (that require further study)	Melatonin
	Thalidomide
	Oxandrolone
	Ghrelin
	Antimyostatin agents

Behl D et al Expert Opin Pharmacother, 2007;8:1085-10

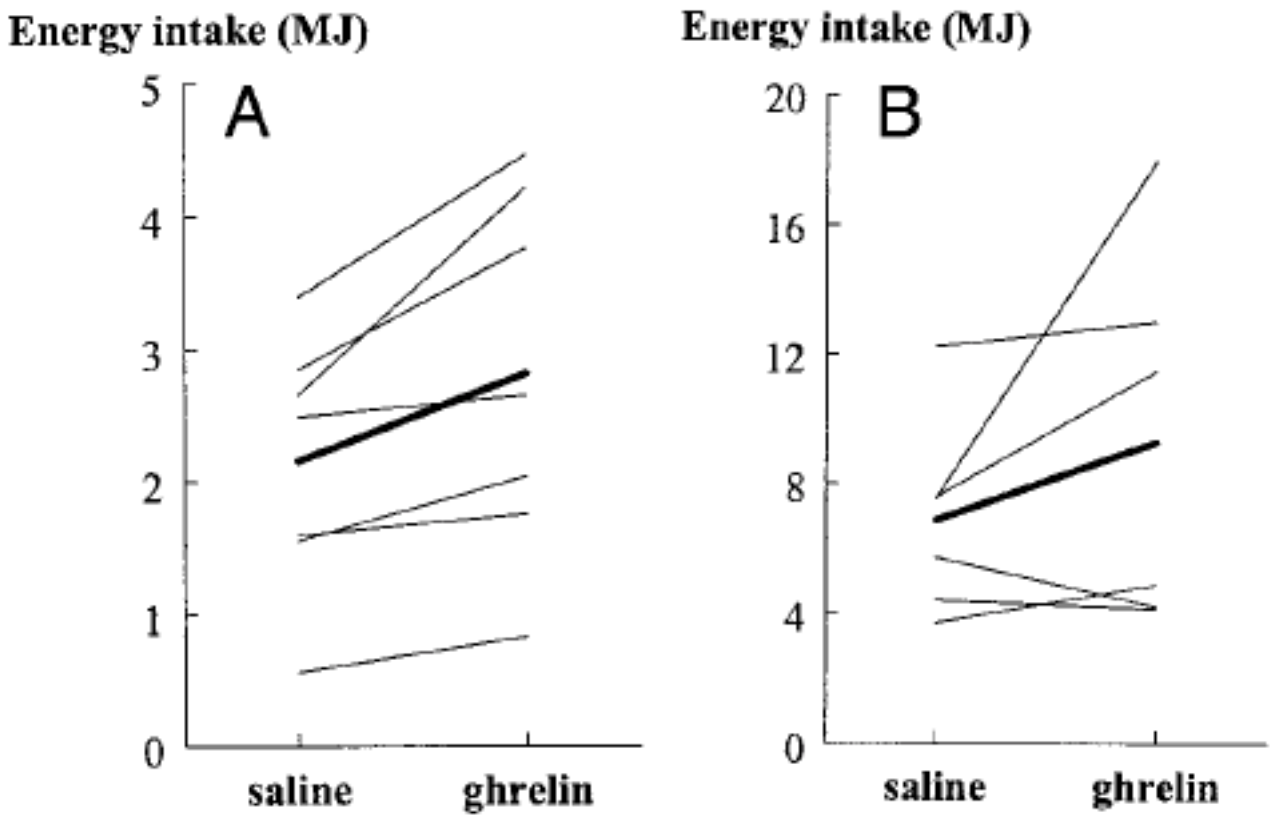
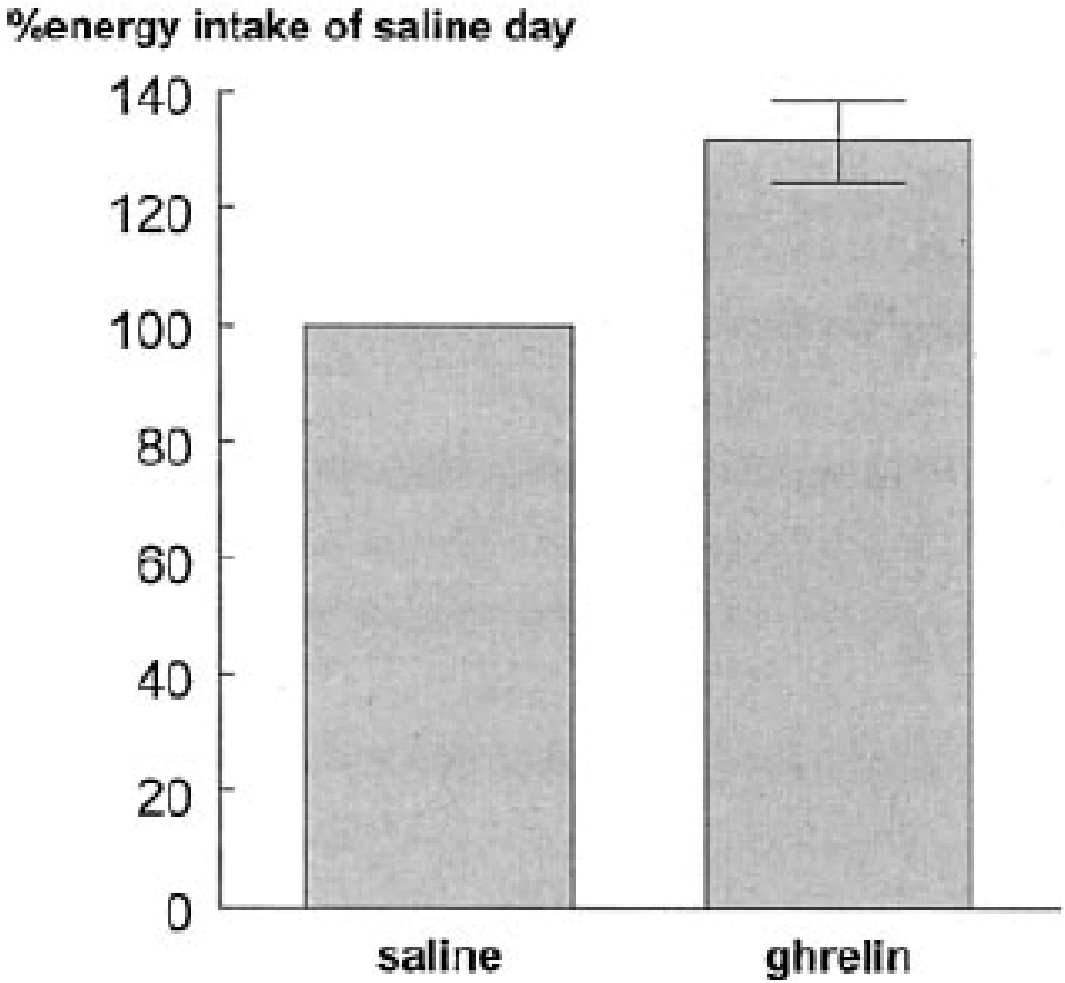


FIG. 2. Energy intakes (megajoules) in individual subjects receiving ghrelin compared with saline infusion. The *bold line* represents mean energy intakes. A, Energy intakes for the buffet meal (n = 7). B, Energy intakes for the 24 h after ghrelin or saline infusion (n = 6, as one patient failed to complete the diary).


%energy intake of saline day
140
120
100
80
60
40
20
0
saline
ghrelin