Anorexia-Cachexia Syndrome

주 영 돈

인제대학교 의과대학 혈액종양내과

Introduction

- Cancer Cachexia
  - Condition of advanced protein calorie malnurition
    - Anorexia
    - Involuntary weight loss
    - Tissue wasting
    - Poor performance
    - Death

Cancer Cachexia

- Clinical wasting syndrome
- Weakness, continuous loss of weight, fat, muscle
- Loss of appetite
- Occur in majority of advanced cancer patients
- Occur in people who are eating enough
- Not related to tumor size, type, extent

Nutritional Problem in Cancer Patients

Malnutrition
: major cause of illness and death in cancer patients

- Too little food to continue body's function
- Progressive wasting
- Weakness
- Exhaustion
- Lower resistance to infection
- Problems tolerating cancer therapy

Cause of Malnutrition

Effect of Tumor (1)

- Stomach, esophagus, intestine
  : nausea, vomiting, poor digestion, poor absorption
- Ovaries, genital and urinary organ
  : ascites → early fullness, fluid and electrolyte imbalance
- Pain caused by tumor
  : anorexia
- CNS tumors
  : confusion, sleepiness → loss of interest in food

Cause of Malnutrition

Effect of Tumor (2)

- Changes in the body's metabolism
  : tumor cells often convert nutrients to energy in less efficient ways than do other cells
- Production of chemicals that cause anorexia and cachexia
  : substance that changes sense of taste
  substance that affect brain satiety center

Cause of Malnutrition

Effect of Cancer therapy

- Direct effect : postop poor protein and fat absorption
- Indirect effect: increased need for energy due to infection and fever

- **Surgery**
- **Chemotherapy**
  - anorexia, nausea, vomiting
  - inflammation and sore in mouth
  - changes of food taste
  - infection
- **Radiation therapy**
- **Immunotherapy**
  : fever, tiredness, weakness → loss of apetite, nutrient need↑

Cause of Malnutrition

Mental and Social Effect

- Eating is an important social activity!
  : anorexia and food avoidance → social isolation
  depression, anxiety, anger, fear → anorexia
- Living alone, an inability to cook or prepare meals, inability to walk to the kitchen
  : → eating problem
- Changes in taste
  : favorite food may not be available, not be tolerated well
- Less eat → weaker → the more seems that cancer is progressing : affects QoL, social paticipation, attitude
- Exercise (walking, mild aerobics)
  : positive effect on the patient's well-being sense

Extent of weight loss in cancer patients at the time of initial diagnosis and its effect on survival after antineoplastic therapy

Type of Cancer	No. of Pts.	Wt. Loss at diagnosis(%)	Survival of Pts.	
			With weight loss (wk)	Without weight loss (wk)
Breast	289	36	45	70*
Colon	307	54	21	43*
Prostate	78	56	24	46*
Sarcoma	189	39	25	46*
Lung	590	61	14	20*
Small cell (lung)	436	60	27	34
Stomach	179	83	27	41*

* <.05 versus patients with weight loss

(DeWys et. al. *Am J Med* 1980)

Simple Starvation vs Cancer Cachexia In Metabolism

	Simple Starvation	Advanced Malignant Disease
Presence of mediators	-	+++
Energy intake	↓	↓→
Energy expenditure (resting)	↓	↑
Body fat	↓	↓
Skeletal muscle	→	↓
Liver	↓, atrophy	↑ size, metabolic activity

Mechanism of Cancer Cachexia

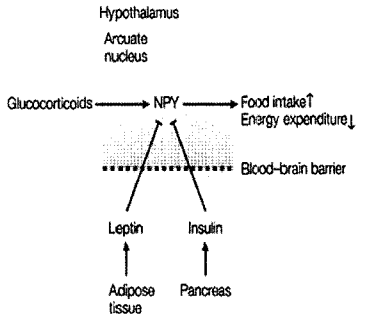
Anorexia

- Factors affect reduction in nutritional intake
  : obstruction of G-I tract, nausea, constipation
  psychological problem
  pain and side effect of cancer therapy
- Even if these factors are well controlled
  early satiety, changes in taste and poor appetite
  : host response to the cancer-bearing state

Mechanism of Cancer Cachexia

Anorexia

- **Leptin**
  - molecule secreted by addipose tissue
  - influence food uptake and energy expenditure via neuropeptidergic effector molecules in the hypothalamus
  - potential role in cancer-related anorexia



Regulation of NPY production in the hypothalamic arcuate nucleus

Mechanism of Cancer Cachexia

Hypermetabolism

- Heterogenous picture of energy expenditure
- Elevated resting energy expenditure
  in some tumor type frequently associated cachexia
- but Total energy expenditure ↓

∴ attempted maintenance of energy balance
through reduced level of activity
→ quality of life ↓

Mechanism of Cancer Cachexia

Substrate Metabolism

- **Carbohydrate**
  relative glucose intolerance
  insulin resistance → glucose production ↑
  glucose turn-over ↑

- **Lipid**
  substantial loss of adipose tissue
  lipogenesis ↓↓
  lipolysis ↑
  serum lipoprotein lipase activity ↓

Mechanism of Cancer Cachexia

Substrate Metabolism

- **Protein**

whole body protein turnover ↑

loss of skeletal muscle protein
skeletal muscle protein synthesis ↓
skeletal muscle protein degradation ↑

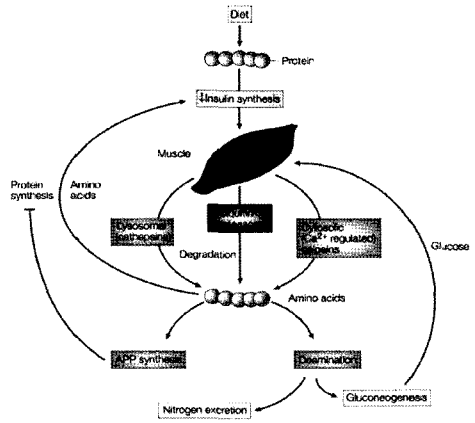
in liver protein metabolism
albumin synthesis – unchanged
fibrinogen synthesis ↑↑

Mechanism of Cancer Cachexia

Substrate Metabolism

- **Protein**

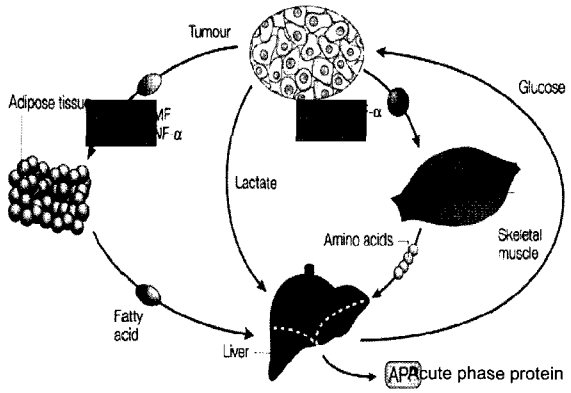
in liver protein metabolism
acute phase protein synthesis ↑
- aid tissue repair, blood clotting, prevention of ongoing tissue damage, destruction of infective organism
- related to accelerated muscle wasting
- associated with shortened survival in cancer patients



Synthesis and degradation of proteins in skeletal muscle

Mediators of Cachexia

- Neurotransmitters: serotonin, neuropeptide-Y
- Cytokines: TNF, IL-1, IL-6, IFN-γ, etc.
- Hormones: cortisol, glucagon, adrenaline, leptin
- *Tumor-specific product*
  : PIF (proteolysis-inducing factor)
  LMF (lipid mobilizing factor)



Cori cycle

Effects of Cytokines on nutrition and metabolism In the tumor-bearing host

- Reduce appetite
- Stimulate basal metabolic rate
- Stimulate glucose uptake
- Stimulate mobilization of fat and protein stores
- Reduce adipocyte lipoprotein lipase activity
- Enhance muscle amino acid release
- Stimulate hepatic amino acid transport activity

Rationale of Nutritional Support

- When nutritional deficiency is corrected
  → morbidity, mortality ↓
- Will the nutritional support preferentially benefit the patient rather than stimulate tumor growth?
- Consensus of opinion regarding the role and efficacy of nutritional support in cancer patients is lacking
- Several studies suggested additional therapies to alleviate tumor cachexia
  megesterol acetate (MA)
  medroxyprogesterone acetate
  eicosanoids
  melatonin

Nutritional Assessment

- Careful history – appetite, weight loss, preferred food
- Physical examination
- Measurement of height and body weight, skinfold thickness
- 24-hour urine collection for measurement of nitrogen
- PB lymphocyte count
- Skin test – delayed hypersensitivity
- Serum albumin, transferrin
- RBC indices for iron status
- Plasma glucose - insulin resistance
- Serum BUN – renal status
- LFT – hepatic function

Enteral Nutrition

- Not demonstrate any consistent benefits of enteral nutrition
- Preferred route of feeding cancer patients
- Proposed benefits of oral and enteral nutrition
  - Maintain gut mucosal mass
  - Maintain brush border enzyme activity
  - Support gut immune function
  - Preserve gut mucosal barrier function
  - Maintain a balanced luminal microflora environment
  - Improve outcome after chemotherapy and radiation Tx.

Suggestions help Cancer patients manage Anorexia

- Small frequent meal (every 1-2 hrs)
- High-protein and high-calorie foods (including snacks)
- Avoid foods low in calories and protein and avoid empty calories (like soda)
- Try to eat when feeling best (usually feel better in the morning and have better appetite)
- Try several different brands of nutritional supplements or high-calorie, high-protein drinks or pudding recipes
- work up an appetite with light exercise (walking), a glass of wine or beer if allowed
- Add extra calories and protein to food (butter, honey or sugar)
- Make eating a pleasant experience (with friends)
- Avoid strong odors, serve cold food instead of hot

Abramson Cancer Center of the University of Pennsylvania

Parenteral Nutrition

- TPN is not associated with improvement of QoL or life span in terminally ill patients with cancer
- Factors need parenteral nutrition
  1. UGI blockage that prevents eating or drinking
  2. Treatment with both CTx and RTx with S/E that limit eating or drinking
  3. Anorexia and/or other problem such as severe depression, *confusion, disorientation*
  4. Problem eating or drinking (odynophagia)

Complication of TPN

- Mechanical
  pneumothorax, air embolism, laceration of subclavian a.
- Metabolic
  hyperglycemia
  electrolyte abnormality – hypokalemia, hypophosphatemia
  abnormality in liver enzyme
- Septic
  catheter sepsis

Glutamine and Arginine

- Glutamine
  non-essential amino acid
  short half-life
  eliminated from TPN
- Change of glutamine metabolism in cancer patients
  principle amino acid used by cancer cell
  → severe glutamine depletion in host
  ∴ conditionally essential amino acid

Glutamine

Randomized trial of glutamine-enriched TPN Vs standard TPN after BMT

Group	No. of patients	Nitrogen Balance (g/d)	No. of patients with clinical infections	No. of patients without positive cultures	Hospital stay (d)
Standard TPN	21	-4.2 ± 1.2	9 (43%)	1 (5%)	36 ± 2
Glutamine-enriched TPN	25	-1.4 ± 0.5*	3 (12%)*	0 (0%)*	29 ± 1*

*$P<.05$ versus standard TPN Ziegler et. al. *Ann Int Med. 1992*

- Prevent the increase in the gut mucosal permeability
  - gut-protective effect of glutamine

van der Hulst et. al. 1993

- In recent studies, controversial

Pharmacologic Therapy

- Steroids
- NSAID – Ibuprofen, Indomethacin
- Progestational agent
  – Megesterol acetate, Medroxyprogesterone acetate
- Pentoxifylline
- Eicosapentaenoic acid

Corticosteroid

- Inhibits PG activity and suppress TNF-α and IL production
- Doses: 5mg t.i.d. prednisolone p.o.
  3-6mg dexamethasone p.o.
  125mg methylprednisolone i.v.
- Produce significantly greater improvement in appetite
- Don't affect weight-loss
- Symptomatic benefits: short-lived
- Adverse effects!

NSAID

- Ibuprofen
  shown to reduce levels of acute phase proteins, IL-6, and to normalize whole-body protein kinetics in cachexic cancer patients
  McMillan et. al. Eur J Surg Oncol 1995
  Preston et. al. Br J Surg 1995
- Indomethacine
  shown to be associated with a significant prolongation in survival of heterogenous advanced cancer patients
  Lundholm et. al. Cancer Res 1994
- Gastrointestinal toxicity!
- Combination with conventional nutritional therapy?

Progestational Agent

- Observations of unwanted weight-gain in patients with breast cancer
- Downregulate synthesis and release of cytokines
- Megesterol acetate
  - Several randomized trial in weight-losing cancer patients : improve appetite and stabilize weight
  - Dose: 240-1,600 mg/day
- Medroxyprogesteron acetate
  - Shown to increase appetite and food intake
  - Dose: 500mg b.i.d. daily
- Side effects: venous thrombosis, peripheral edema

Randomized double-blind placebo-controled trial of cisplatin and etoposide plus megesterol acetate/placebo in extensive-stage small-cell lung cancer; NCCTGS

JCO 1996

- Increased nonfluid weight gain (P = .004)
- Significantly less nausea (P = .0002) and vomiting (P = .02)
- Significant thromboembolic phenomena occurred more often in megestrol acetate versus placebo (9% v 2%, P = .01)
- Inferior response rate to chemotherapy (68% v 80%, P = .03)
- Inferior survival duration (median, 8.2 v 10.0 months, P = .49)
- No significant changes in quality of life scores over time

- CONCLUSION
  : Megestrol acetate cannot be routinely recommended for all patients with small-cell lung cancer at the time of chemotherapy initiation.

Clinical Application

	Corcitosteroid	Megesterol
Life expectancy	A few weeks	Longer period
Weight gain		
Non-fluid	-	+
Lean body mass	-	-
Symptom	Anorexia, asthenia, chronic nausea	Anorexia, change of body image

Pentoxifylline

- shown to inhibit production TNF
  suppress protein breakdown in rat model
- Controlled trial in cancer patients
  : No benefit in terms of appetite or nutritional measures compared with placebo

→ TNF suppression alone
: not sufficient to reverse cachexia

Eicosapentaenoic Acid

- Essential polyunsaturated fatty acid of n-3 class
- Found in large quantity in fish oil
- Action mechanism
  - Anti-inflammatory effect
  - Downregulate acute phase protein response
  - Impair end-organ effects of PIF and LMF by effect on cell signaling
- Animal study
  : weight stabilizing effect in cachexic tumor-bearing mice
- Uncontrolled study
  : weight stabilizing effect in weight-losing pancreatic cancer patients

Br J Cancer 1997

Effect of Fish Oil on Appetite and Other Symptoms in Patients With Advanced Cancer and Anorexia/Cachexia: A Double-Blind, Placebo-Controlled Study

JCO 2003

- No significant differences in symptomatic or nutritional parameters ($P < .05$)
- No correlation between changes in different variables between days 1 and 14 and the fish oil doses.
- Majority of the patients were not able to swallow more than 10 fish oil capsules per day, mainly because of burping and aftertaste.
- CONCLUSION
  : Fish oil did not significantly influence appetite, tiredness, nausea, well-being, caloric intake, nutritional status, or function after 2 weeks compared with placebo in patients with advanced cancer and loss of both weight and appetite.

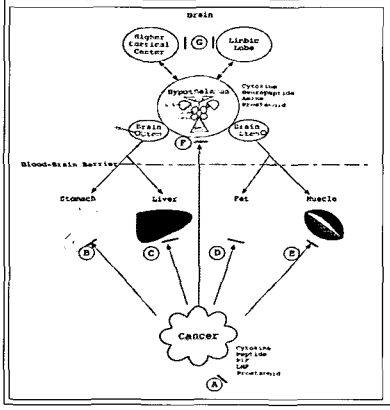
Thalidomide

- Inhibit TNF-α
- It was reported to improve insomnia and restlessness as well as nausea in advanced cancer patients
- It has improved appetite, resulting in well-being sense in 30-50% of patients studied.

Bruera et. al. Ann Oncology 1999

- Advantage: inhibition of tumor growth
  → unique role both as an anticachexic agent and antineoplastic agent

The potential modalities of pharmacological intervention of cancer anorexia-cachexia syndrome



- First-line treatment
  Glucocorticoid FA
  Progesterone FA
- Second-line treatment
  Carabinoids F
  Cyproheptadine F
  Thalidomide A
  β2-agonist E
  Branched-chain AA EF
  NSAID AF
  Metoclopromide BF
  Eicosapentanoic acid ADE
  Fluorouridine A
  Melatonin A
  Others
  Anabolic steroid E
  Pentoxifylline A

Conclusion

- Malnutrition is major cause of death of cancer patients
- There are no clear nutritional recommendations yet
- It is generally recommended
  Megesterol acetate: long-term use (weeks to months)
  Glucocorticoid: shorter period use
- Primary benefit: increased appetite and weight gain
  But not improved survival or quality of life
- Progress in the future
  1. Define the subgroups of cachexia and identify those patients who will benefit from available therapy
  2. Develop new drugs – melanocortin antagonist, cytokine antagonist
  3. combined multimodal therapy
     – nutritional support + inflammatory modulation