Chapter 1

BACKGROUND AND LITERATURE REVIEW

Introduction

Advanced incurable cancer patients suffer not only from various organ involvement and dysfunction by primary disease but also from many remote effects of cancer. One unique problem that causes physical and psychological retardation to these patients is the anorexia-cachexia syndrome. Cancer anorexia-cachexia can be defined as a state of severe decrease in appetite and marked body weight loss in cancer patients that may not relate to direct cancer involvement of digestive system. In 1980, Eastern Cooperative Oncology Group Study [1] found that 31% of non-Hodgkin's lymphoma patients had weight loss and up to 87% of gastric cancer patients had premorbid weight loss. Patients with weight loss had shorter median survival time and a poorer response to chemotherapy. So premorbid body weight was recognized as an important prognostic factor.

Cancer anorexia-cachexia has two main features [2-4]. First is anorectic state that is severe enough to cause cachexia. Cancer itself can produce anorexia by direct invasion of the digestive system, producing anorectic substances or causing cytokines secretion from host cell [5]. In addition therapeutic modalities and patients' emotion also contribute to anorectic state. Second is altered host metabolism that leads to body energy imbalance and weight loss.

Metabolic Change in Cancer Cachexia

Change in carbohydrate metabolism is observed from many studies. Increase glucose synthesis [6], insulin resistance [7], decrease glucose tolerance [8], and increase gluconeogenesis [9-10] lead to a diabetic liked state in cancer cachexia patient. There was evidence that glucose consumption was increased by tumor cell but ineffective [11]. Implication for treatment was shown by the data that endogenous glucose production in cancer cachexia patients was suppressed by the insulin infusion at a high physiologic rate[12]. Glucose synthesis from alanine, glycerol, and lactate is also increased in patients with progressive cancer [10,13].

Much of evidence supports that tumor cell requires amino acid for its growth [14-16]. Increased host proteolysis [17,18] and increased whole-body protein turnover are the hallmark of cancer-cachexia. Decreased protein synthesis and increased degradation of protein result to hypoalbuminemia [19]. Reduction of protein mass, atrophy of skin and skeletal muscle, and hypoalbuminemia are the end results of altered host protein metabolism. These alterations have many significant clinical influences such as impaired wound healing, susceptibility to infection, and poor performance status.

The major contribution for weight loss in cancer-cachexia is the fat loss. Significant changes include accelerated glycerol and fatty acid turnover [20] and decreased lipogenesis [21]. Decreased lipoprotein lipase activity, elevated triglycerides, and decreased high-density lipoproteins may cause hyperlipoproteinemia in cancer [22,23].

The data about energy expenditure showed contradictory results. Some studies indicated that basal metabolic rate (BMR) was increased [24,25]. While the others stated unchanged [26] or decreased BMR in patient with cancer cachexia[27].

Mediators in Cancer Cachexia

Several cytokines were thought to be the candidate for causing anorexia-cachexia. TNFα can increase energy expenditure, lipolysis, and protein turnover [28] when presents. In animal model, slowly continuous infusion of TNFα could caused cachexia[29]. However, the attempts to demonstrate the consistent elevation of TNFα failed to support the cause and effect relationship in cachectic patients with cancer [30-32]. IL-1 can increase whole-body protein turnover and induce degradation of muscle protein [33]. IL-6 may be an effector of the wasting process by IL-1 [34]. Interferon-γ has many effects that are similar to those of TNFα on fat metabolism, such as inhibition of lipoprotein lipase, decreased protein synthesis, and increased fat breakdown [35,36]. All of these cytokines have not been found to be consistently raised in patients with cancer anorexia-cachexia.

One potential non-cytokine mediator of cachexia was recently identified as 24-kDa proteoglycan [37] which caused cachexia in mouse without anorexia. The same substance was also found in the urine of patients with cancer-cachexia. The major effect of this mediator was to accelerate muscle degradation which resembled the change of cachectic state in cancer patients.

Clinical Features

Cancer anorexia-cachexia syndrome is commonly found in patients with gastrointestinal malignancies and also frequently occurred in non-gastrointestinal malignancies [38]. It was almost invariably encountered in advanced state of cancer, 80% [39]. Up to 15-40% could be found at presentation [40,41]. The main symptom is early satiety which has an incidence of 40-60% in these cases[42].

Body composition studies in cancer cachexia revealed the wasting of body fat and loss of muscle mass with sparing of visceral organs[43,44]. Protein and calories

depletion in patient with advanced cancer caused reduction in fat and fat-free mass [45]. Body fat and body cell mass were decreased while there was increasing extracellular mass in malnourished patients[46]. However, there were contradictory result in studying the body compartment. One study found no difference in body composition studies between benign and malignant gastrointestinal disease [47].

Management Of Cancer Anorexia-Cachexia Syndrome

Theoretically the best management for cancer anorexia-cachexia should be the treatment which has a direct effect on tumor. However in most cases, treatments of cancer are not so effective because of the advanced stage of disease and poor response to an available treatment. In the past, many palliative measures for cancer anorexia-cachexia were prescribed to alleviate this suffering symptom. In general, these measures can be divided in to two groups. One consists of supportive nutrition, enteral or parenteral route, the other is the pharmacologic approach to increase appetite and body weight. Brief details of these measures are discussed below.

Supportive nutrition

By providing adequate nutritional support, enteral and parenteral nutrition would result a positive energy balance and overcome weight loss. Unfortunately, enteral nutrition is frequently inaccessible in most cancer patients due to gastrointestinal involvement of primary or metastatic tumor. Moreover, some data showed that the enteral or parenteral nutrition alone might not alter the progressive weight loss [48]. In addition, pooling data suggested that the parenteral nutrition did not provide any significant benefit in term of overall survival. Although slight improvement in short term survival and minimal increment of response to chemotherapy could be anticipated from these supportive measures. The most major drawback is the greater risk of access related complications, i.e. catheter-related infection [49].

Pharmacological Approach

Many agents were previously tested in cancer anorexia-cachexia. Most studies concerned objective improvement in term of weight gain and appetite stimulation.

Hydrazine sulfate

Previously hydrazine sulfate was thought to be an experimental cytotoxic, antineoplastic drug. A controlled trial from CALGB found no differences in the degree of anorexia between treatment and placebo group [50].

Metoclopramide

Metoclopramide is a prokinetic agent that may relieve anorexia and early satiety [51]. Some patients might take benefit from metoclopramide by decreasing anorectic state but there was no significant weight improvement observed.

Dexamethasone

Dexamethasone can be used as an appetite stimulator and to increase the well being of cancer patients[39]. A double-blind crossover study with 4-6 mg/d dose could improve patient's appetite without significant side effects[52,53] . However adrenal suppression and decreased immunity make this agent unattractive for a long term use.

Tetrahydrocannabinol

Tetrahydrocannabinol (THC) can be used as an antiemetic and an appetite enhancer [54]. A crossover study in weight loss patient revealed a small promotion of body

weight [55]. When used at 15 mg/d dose, THC caused significant side effects, such as dizziness, fluid retention, somnolence, and dissociation in elderly.

Pentoxifylline

Pentoxifylline is a methylxanthine derivative that was reported to lower TNF mRNA levels in cancer patients and decrease replication of HIV. Trial using pentoxifylline as an anti-TNF agent in cancer cachexia by Goldberg et al [56] showed an indifferent effect when compare with placebo concerning weight gain or increased appetite.

Cyproheptadine

Known as an histamine with appetite enhancing effect, cyproheptadine was also used to treat cancer cachexia. Kardinal et al [57] compared cyproheptadine with placebo in advanced cancer patients. Mild increased appetite, less nausea and vomiting were observed in the treatment group. But cyproheptadine did not significantly halt the progression of weight loss. Minor side effects, sedation and dizziness, were found in treated group.

Megestrol Acetate

From all above available agents, there was no any safe and effective agent which could improve patient from cancer anorexia-cachexia. As a synthetic progestogen, megestrol acetate is firstly used in hormone responsive cancers. Initially, weight gain was found to be an adverse effect, which was subsequently found to be useful, in treated patients[2]. Megestrol acetate is a potent progestrogen which has no androgenic or estrogenic properties. It has a slight but significant glucocorticoid effect and a very slight mineralocorticoid effect. Peak plasma concentration occur 1-3 hours after oral administration. Urinary excretion as metabolites is the major route of excretion, 57-78%.

Half-life is 15-20 hours. Available forms in Thailand include 40-mg tablet and 160-mg tablet. Increasing use is to abate anorexia-cachexia in cancer or HIV infection. The true mechanism of action of the agent is still not elucidated but publications that confirm this role are substantial.

Tchekmedyian et al [2] observed marked weight gain and appetite enhancement in breast cancer patients who received high dose of megestrol acetate treatment, 480 to 1600 mg/d, and suggested the possible role of megestrol acetate in reversing cancer cachexia. This effect was not related to stage of disease or response to treatment. Loprinzi et al [58] demonstrated a benefit of megestrol acetate over placebo in cachexia patient in term of weight gain. The megestrol acetate group had a significant improvement on weight gain and appetite enhancement more than the placebo group while side effects were minimal and acceptable. Another study from Tchekmedyian et al compared the conventional dose of megestrol acetate, 160 mg/d, versus placebo and gave the same results [59] . Very short term effects of megestrol acetate trial by Bruera E, et al [60] also revealed objective improvement of nutritional status and appetite stimulation. These studies supported the usefulness of megestrol acetate in improving patient's body weight in cancer anorexia-cachexia. Only one previous study in Thailand by Tepmongkol et al [61] was a non-randomized, single arm, conventional dose of megestrol acetate,160 mg/d, in various advanced malignancies. Results also confirmed the efficacy on weight gain and improvement in patient's performance status.

The optimal dose of megestrol acetate is undetermined at present. Gebbia et al [62] studied the difference between 160 and 320 mg/d dose and found no significant difference between both arms on appetite or weight gain. Although the higher dose arm seemed slightly better in increasing appetite and weight. The dose more than 480 mg/d was found to have no greater benefit so a lower dose was recommended as an initial dose. Loprinzi et al [63] found a positive correlation between increased body weight and increased dose of megestrol acetate with non-fluid component of weight gain. Starting

with 160 mg/d dose was advised and then dose escalation should be considered after failure to increase weight in routine clinical practice. Kornblith et al [64] studied cases of hormonal responsive breast cancer with 3 different dose levels, 160, 800, and 1600 mg/d of megestrol acetate. They concluded that the conventional dose, 160 mg/d, seemed to have less side effects, better physical functioning, less psychological distress, and better improvement of overall quality of life. So the conventional 160 mg/d dose was recommended as an appropriate initial dose. It should be noted that all of these studies were conducted at the lowest dose of 160 mg/d of megestrol acetate. Most studies recommended the lower dose as the starting dose.

From one study, Major change of body composition by megestrol acetate treatment was increasing body fat [65]. Although weight gain and fat accumulation would not imply a better survival benefit, it is somewhat important concern of patients who have considerable weight loss and family.