Chapter 3

# RESEARCH METHODOLOGY

## Research Design

Two arms open labeled randomized trial.

## Research Methodology

Fifteen consecutive cases of cancer anorexia-cachexia in each arm were investigated for response to megestrol acetate in term of altered body weight, appetite and quality of life assessment, and anthropometric measurements.

## Sample Size Justification

This trial was designed to detect difference in mean weight gain at least 4.5 kgs between two study arms with different doses. Previous study[61] showed mean weight gain of 2.976 kgs by 160 mg/day dose of megestrol acetate with SD = 5.024. One-sided test with the $\alpha$ error equals to 5% and the $\beta$ error equals to 20%. Number of patients in each arms can be calculated by following equation:

$$n / group = 2 [ (Z_\alpha + Z_\beta) \sigma ]^2 / (Mc - Mt)^2$$

Approximately 15 patients in each arms are required.

## Patient Eligibility

Patients with history of weight loss in association with cancer were interviewed by the principle investigator for justification of enrollment which was followed the below criteria.

*Inclusion criteria*

1. Patients were advanced incurable and non-hormone responsive cancer.

2. Each patient should have history of significant weight loss defined as weight loss 10% or more from baseline in patients with premorbid normal to underweight by body mass index (<25 $kg/m^2$) and 20% or more from baseline in patients with premorbid overweight by body mass index ($\geq$25 $kg/m^2$).

3. Performance status according to Eastern Cooperative Oncology Group (ECOG) of the individual patient was not more than 2 (see appendix I).

4. Patients' expected survival was more than 3 months.

5. Signed informed consent should be done by every patient.

*Exclusion criteria*

1. Ascites or lower extremities edema was not detected.

2. Receiving enteral or parenteral nutrition was contraindicated.

3. Known mechanical obstruction of the alimentary tract, malabsorption or intractable vomiting patients were prohibited.

4. Concurrent or planned treatment with steroids, estrogen or other progestational agents and known directed appetite stimulants could not be prescribed to the patients.

5. A patient had history or evidence of thromboembolic disease within previous 6 months, poorly controlled hypertension or congestive heart failure, pregnant or nursing women.

6. A patient had a seropositive anti-HIV testing or clinically indicated symptomatic HIV infection.

Experimental Maneuver

Before randomization patients were stratified by primary disease site, sex, and concurrent treatment. Then patients were randomly allocated into 2 groups, the low dose (40 mg/day), and the conventional dose (160 mg/day) megestrol acetate therapy group. Megestrol acetate will be provided in 40 mg or 160 mg tablet preparation. Therapy continued for at least 4 weeks unless serious toxicities occur or patients refused to receive further therapy. If intolerable toxic reactions or excessive weight gain, more than 10% over premorbid weight, were attributed to the medication then the therapy was stopped.

Data Collection

Baseline body weight and height were measured and laboratory variables were done. Every 4 weeks evaluated schedule include body weight , mid-arm circumference, triceps skinfold, performance status, appetite and quality of life assessment score, and laboratory parameters including complete blood count, BUN, creatinine, electrolytes, fasting plasma glucose, liver function tests, serum albumin and total protein.

Monthly assessment of body weight and body compositions by anthropometric measurements was evaluated by the same physician. The methods of measurement were adjusted to be consistent and reliable ( see appendix II ). Body mass index was calculated by using equation:

$$BMI = weight/height^2 \ (kg/m^2)$$

Anthropometric measurements, mid-arm circumference (MAC [mm] ) and triceps skin-fold thickness (TSF [mm] ) was measured on the right arm. Muscle mass was evaluated by calculation of mid-arm muscle circumference (MAMC) and mid-arm muscle area (MAMA). Mid-arm circumference was calculated from the equation:

$$MAMC = (MAC - [\pi \times TSF]) \quad \text{all in centimeters unit.}$$

Mid-arm muscle area ( $mm^2$) was calculated from the equation:

$$MAMA = ([MAC - (\pi \times TSF)])^2/4\pi \quad \text{all in millimeters unit.}$$

Total body fat mass was estimated by mid-arm fat area (MAFA) as equation:

$$MAFA = \{ ([TSF \times MAC]/2) - (\pi \times [TSF]^2)/4) \} \quad \text{all in millimeters unit.}$$

The appetite and quality of life assessment were measured by Functional Assessment of Cancer Therapy score by each patients with assistance of research nurse or physician if needed ( see appendix III ).

## Data Analysis

*Analysis*

Each arm was tested for any difference in term of mean percentage of body weight gain and anthropometric measurements by independent t-test method at significant level p=0.05.

The other outcomes to be measured were appetite score and quality of life score by comparing change of pre and post study score by independent t-test method at significant level p=0.05.

*Definition of analysis population*

All patients registered in the study should be accounted for analysis. Patients who were not evaluable, who died or withdrew before termination of the study must be specified and followed up. Analysis included patients that had completed at least 4-week period of study.

## Ethical Consideration

Because all of patients included in this study were cases of advanced incurable cancer, palliative treatment with megestrol acetate should not cause any difference in term of survival outcome. In cases that had good response to megestrol and completed study, continuation of treatment was discussed individually with the patient. Some unaffordable patients could further medication provided by investigator as long as he or she came to follow up. In cases that had poor response, termination of medication was recommended.

## Limitations of the Study

Patient's compliance was assessed from returning pill counted because there was no available blood or urine level of tested drug. Other confounding factors that could not be included in stratification were patient's socioeconomic background and dietary variation. These factors might have influences on body weight. The study could not be double blinded fashion because unavailable placebo. This might cause some biases on the results of patient assessment.