Cachexia–Anorexia–Asthenia

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Abstract
The National Cancer Institute (Canada) sponsored a workshop on symptom control in Banff, Alberta, in October 1993. This article reports on the workshop recommendations for research on one symptom complex, the cachexia–anorexia–asthenia syndrome. In addition to encouraging study generation, the recommendations provide a baseline for assessing the scope and strength of future Canadian research initiatives on cachexia–anorexia–asthenia. J Pain Symptom Manage 1995;10:151–155.

Key Words
Cachexia, anorexia, research workshop

Introduction
Weight loss, asthenia, and anorexia, often associated with chronic nausea, are among the most common symptom problems afflicting patients with advanced cancer.1 Earlier, pre-chemotherapy studies suggest that weight loss and associated metabolic abnormalities may account for 25% of cancer deaths.2 As patients with cachexia–anorexia are often weak and unable to care for themselves, family resources are severely taxed, and patients often require institutional care for prolonged periods prior to death.

The term “cachexia–anorexia syndrome” is used somewhat loosely, as the defining qualities of the syndrome and the consequent tests that monitor progress or regression remain imprecise. There is a Chinese proverb that states “The beginning of wisdom is to call things by their right names.”3 A modern coiner of aphorisms, Sir Peter Medawar has said, “No new truth will declare itself from inside a heap of facts.”4 At present, a “heap of facts” garnered by research workers working in disparate areas is available to the clinical investigator concerned with cancer cachexia. The web connecting these observations in a coherent mosaic, however, remains to be fully woven. Some salient features stand out, however, including

1. The cachexia–anorexia complex has a variable incidence depending on the type of primary tumor.4 It is relatively uncommon in patients with one form of adenocarcinoma, breast cancer, while it is very common in certain other forms of adenocarcinoma such as lung cancer and pancreatic cancer. Wasting is not commonly observed in the hematologic malignancies although myelodysplastic syndromes are often associated with extreme wasting.

2. Studies comparing the biology of those tumors that show a propensity to develop cachexia–anorexia with those that do not, remain to be carried out. The syndrome is
probably caused by chemical factors produced as a result of a host response or directly by the tumor. A number of cytokines that can produce symptoms mimicking the cachexia–anorexia syndrome have been identified. The list includes tumor necrosis factor, interleukins 1 and 6, and interferon γ. However, specific cytokine abnormalities have not been linked to cancer cachexia–anorexia in humans, and noncytokine chemical factors have also been implicated. We presume that an interactive cascade involving multiple chemical factors is responsible.

3. Metabolic abnormalities may precede weight loss in animal cachexia–anorexia tumor models, and it is presumed that the same phenomena occur in humans. While subsequent decrease in nutrient intake will compound the problem, loss of appetite appears to be related to the onset of these metabolic abnormalities, rather than acting as a primary cause of the cachexia–anorexia syndrome.

4. Clinicians must be careful to diagnose those situations where cancer patients lose weight because of simple starvation, potentially corrected with parenteral or enteral nutrition, rather than assigning all changes in weight to the cachexia–anorexia syndrome. Correctable examples include some patients with head and neck cancer with obstruction of the upper digestive tract, and some patients with ovarian carcinoma with intermittent small-bowel obstruction. Notwithstanding the occasional patient who is truly starving, the vast majority of cancer patients who lose weight suffer from a complex metabolic aberration that does not respond to simple replacement of nutrients. A number of studies have demonstrated that replacement of calories using standard enteral or parenteral diets does not result in meaningful weight gain or improvement in quality of life or tumor response. It remains to be determined whether the use of special dietary supplements directed at correction of specific metabolic abnormalities will change the current wisdom that dietary supplementation does not help patients with the cachexia–anorexia syndrome.

5. Similar to the observations made with diet, drug trials attempting to increase appetite and weight generally have not been successful. Corticosteroids certainly produce an immediate improvement in appetite and occasionally in weight, but the effect is usually short-lived. However, the observation that progestational agents can improve appetite and reverse weight loss is possibly of major importance. It remains to be clearly determined whether the immediate improvement in patient well-being produced by progestational agents translates into longer-term improvements in patient energy, mobility, and independence. However, for the first time pharmacologic therapy has significantly impacted upon the cachexia–anorexia syndrome, thus creating the impetus to “work back” from the clinical observation to the laboratory to determine how these agents work. Consequent understanding of an exploitable lead may result in development of more specific agents. The use of progestational agents in combination with other drugs that are relatively ineffective when used alone or with special diets may offer a promising area for future study.

The McMaster Loop provides a useful framework for assessing the importance and feasibility of a research initiative. The cachexia–anorexia complex certainly presents an extraordinary burden for involved patients, families, and society. While its pathophysiology remains to be fully elucidated, sufficient information is available to frame studies linking the laboratory and the bedside. Successful pharmacologic intervention with progestational agents provides a base for immediate projection of further clinical interventions, which could be carried out at reasonable cost and with reasonable anticipation of success. This success could be measured both in terms of alleviating suffering and reducing health-care costs. The lessons learned from these studies, in turn, will lead to more-sophisticated approaches to the cachexia–anorexia syndrome.

Participants at the National Cancer Institute Workshop concluded that we do not need to wait for further clarification of the pathophysiology of the cachexia–anorexia syndrome before launching a coordinated series of clinical studies. The design and conduct of these studies will be enhanced if investigators can agree upon a taxonomy codifying the various aspects of the cachexia–anorexia syndrome. Adoption of a standard battery of assessment techniques should also be considered. Protocols should not only consider biologic issues but must also encompass considerations of the
impact of interventions on health-care costs, both to society and the family, and assessments of the effects of therapy on patient/family quality of life.

Following presentations on the pathophysiology, assessment, and current clinical management of cachexia-anorexia, the participants discussed a series of strategies that, with support, could be successfully introduced without delay. The workshop recommendations are listed below.

**General Recommendations**

**Asthenia–Anorexia–Anorexia in Cancer Patients**

1. The cachexia–anorexia–asthenia syndrome should be assigned a high priority for research support as it (a) devastates family relations and makes the patient dependent upon family and health-care institutions; (b) results in a requirement for expensive medical care; and (c) is a promising target for intervention which can reduce patient–family suffering and the associated high costs of care during the last days of life.

2. Cancer control represents a series of preventive strategies. In keeping with this concept, research interventions should be available to patients early in the trajectory of the cachexia–anorexia–asthenia cascade. For this to occur, (a) cancer centers should recognize that anticancer therapy goes beyond destructive therapeutic modalities and encompasses approaches aimed at altering tumor biology and associated symptoms, and (b) cancer centers should create a milieu wherein studies on symptom control can flourish.

3. Family studies demonstrate that the cachexia–anorexia–asthenia complex ranks at the top of physical causes of suffering and contributes to psychosocial distress. The priorities of patients and families should be reflected in cancer research studies.

4. Consonant with this observation, cancer research outcome measures should emphasize (a) improvement in function and (b) satisfaction with therapy.

5. While laboratory scientists are making progress in elucidating the pathophysiology of the cachexia–anorexia–asthenia complex, their studies are not sufficiently linked in a continuum with clinical research. Conversely, clinical research leads, such as the effect of progestational agents on the cachexia–ano-
rexia–asthenia complex, have not been sufficiently applied to laboratory models. Priority should be assigned to studies bridging the two research realms.

6. Expertise relevant to the cachexia–anorexia complex is found in disciplines as yet not involved in cancer research. Proposals that recruit this expertise in coordinated studies should be encouraged.

7. The mechanisms of the cachexia–anorexia–asthenia complex may vary from tumor to tumor. For example, muscle weakness and fatigue are common in advanced breast cancer patients, but weight loss is relatively uncommon. Efforts should be made to enroll patients, from specific disease categories.

**Specific Recommendations**

**Taxonomy**

The descriptive terminology and staging of the cachexia–anorexia–asthenia complex are not sufficiently defined. The formation of working groups to develop a taxonomy that can be subsequently used in research studies represents an early priority for action.

**Assessment**

The NCI-CCS should support a workshop to establish a standard assessment panel for studies on the cachexia–anorexia–asthenia complex. Colleagues to be invited who are usually not involved in cancer research include:

- Neurologists knowledgeable in muscle studies
- Geriatricians, physiotherapists, and occupational therapists knowledgeable in function assessment
- Nutritional experts knowledgeable in the analysis of body composition and nutrients
- Health-care economists
- Family/patient representatives

Categories for assessment may include:

- Changes in patient function (psychosocial and physical)
- Cost–benefit studies
- Changes in body composition
- Measurement of select metabolic abnormalities
- Measurement of associated neurologic abnormalities
- Measurement of associated immunologic abnormalities

While the suffering dimension of the cachexia–anorexia–asthenia complex is well established, the economic costs are less clear. The NCI-CCS should encourage baseline studies on associated health-care costs.

**Therapy**

The impact of progestational agents on the cachexia–anorexia–asthenia complex may be an observation of seminal importance. As good animal models of tumor cachexia exist, studies of the effects of progestational agents and related anabolic agents in these models should be encouraged.

Clinical studies involving the following pharmacologic strategies should be encouraged:

1. Progestational agents (P.A.)—stress outcomes on patient function and family life
2. Anabolic steroids—comparison with progestational agents
3. Dietary interventions involving omega-3 fatty acids (menhaden oil) and branched-chain amino acids
4. Combination approaches
   - P.A. plus cannabinoids
   - P.A. plus dietary supplements
   - P.A. plus prokinetic agents
   - P.A. plus central nervous system (CNS) stimulants (for example, methylphenidate in asthenic patients)

Sufficient information is already available from research on the cachexia–anorexia–asthenia complex to be applied in our clinics. A working group should be commissioned to bring forward clinical guidelines for the current assessment and management of patients in cancer centers and the community.

**Follow-Up**

An audit of the disposition of research-strategy proposals should be carried out:

Process:

- Generation of research proposals
- Response of CCS–NCI and other agencies to these proposals
- Monitoring of Canadian studies and grants panel responses
Outcome:
• Publication of statements from granting agencies lending encouragement to researchers to develop multidisciplinary coordinated proposals
• Publication of health professional guidelines
• Review of literature citation
• Review of subsequent practice change

References