Clinical Trials for the Treatment of Secondary Wasting and Cachexia

Working Group Session Report: Cancer

Discussion Group Leader: Steven Hirschfeld
Food and Drug Administration, Rockville, Maryland 20852

Weight loss, anorexia, and pain are common symptoms in patients with malignancies. These are complicated by the sensation of dry mouth, early satiety, depression and taste change (Curtis et al. 1991, Curtis and Walsh 1993). The net effect on the patient is a decrease in performance status, a decreasing ability to recover from the effects of therapy, and an increased tendency to immune suppression, opportunistic infections and potentially lethal events (Albrecht and Canada, 1996, Tisdale, 1997).

The nutritional status of a patient can generally be assessed by various modalities including history, physical measurements, declines in serum levels of albumin, transferrin, declines in total body nitrogen and potassium, and decreases in immune response. These are typically not incorporated into routine cancer patient care, with the greatest reliance placed on global assessment and loss of body weight (Delmore 1997).

The assessment of cancer patients for nutritional status is highly variable in clinical practice, and is commonly not included in the evaluations associated with research protocols. Among the reasons there are difficulties in the interpretation of many tests are:

1. Accumulation of fluids in body compartments
2. Changes in the tumor mass
3. Alterations in hormonal status due to therapy or paraneoplastic phenomenon (Gold et al., 1996)
4. Effects of anti-cancer therapy including emesis, anorexia, fatigue, depression, tissue damage to the liver, kidney, and other critical organs
5. Effects of therapy for supportive care including nausea and alterations in bowel motility and function

Any of these can lead to ambiguities in the interpretation of most measurements. A simplified categorization of assessment tools is in Table 1.

Which of these modalities are useful for assessing cancer patients? Potentially all depending upon the context; however, there are certain questions that bear directly on clinical management and possible interventions related to malignancies. The questions and some available means to assess them are displayed in Table 2.

With few exceptions, the treatment of malignancies relies upon multiple cycles of multiple treatments, often using different modalities. There is a generally accepted consensus that delays or reductions in the intended therapeutic plan reduce the likelihood for a positive outcome, even if the outcome is palliation of symptoms. In addition, most cancer therapies can manifest multiple and even severe toxicities that will affect any assessment and confound the interpretation of a diagnostic test.

For these reasons, the participants in the oncology discussion group agreed on a reduced set of three categories to functionally describe wasting in cancer patients. These are:
1. The rate of undesired loss of weight
2. Decrease in performance status
3. Increase in time to recovery of function following a cycle of therapy

Assessments of the rate of weight loss should be by global assessment combined with anthropometry, which in its simplest form would be weight, height, mid arm circumference and calculation of body mass index. Weight loss of >5% in 30 days or <10% from pre-morbid could be considered a sign of wasting. If there is a perceived need during a research study to assess body composition, the technique used should be confirmed by another modality. As a specific example, the use of bioelectric impedance results in two measurable parameters, capacitance and inductance. These are interpreted according to mathematical transformations into percent body fat and lean body mass, where the assumption is that the fluid compartment is primarily lean body mass. In cancer patients, who are prone to develop extravascular fluid collections, and in addition have a tumor mass that should not be considered as part of the lean body mass, the applicability of the standard transformations is not valid. If bioelectric impedance is used, therefore, there must be determination of body composition by another technique. This independent verification will then guide what transformations of the capacitance and inductance measurements should be used, and if any changes in measurement are due to an increase in lean body mass, a change in fluid accumulation, changes in tumor burden, or some combination.

The second category of change in performance and functional status could be measured by any technique that would meet three criteria—the technique must be patient specific, sensitive to the parameters being measured, and validated in

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another patient population with similar characteristics to the study patients. Consistency in the timing and mode of administration is important.

The third category of increase of time to recovery from the previous treatment cycle may be the most important regarding the likely success of any treatment plan. Interventions that prevent or reverse this parameter are particularly relevant to therapeutic outcome.

Attempts to reverse the decline of cancer patients solely by supplemental feedings has been challenging and has had mixed results (Bozetti 1994, Harrison and Brennan 1995, Hill and Daly 1995, Koretz 1984, Mercadante 1998, Mulligan and Bloch 1998, Nixon 1996, Pistersm and Pearlstone 1993, Torosian and Daly 1986). The most aggressive form of supplemental feeding is parenteral nutrition. The outcome results of patients with malignancies who received parenteral nutrition are informative. Parenteral nutrition has no effect on the ability to tolerate radiation, but has been documented in some studies to have a modest effect on the ability to tolerate some forms of chemotherapy and surgery. Studies on rodent models of human tumors suggest that in some cases tumor burden may increase at the expense of the host as a result of supplemental nutrition.

There is a need for interventions that would decrease the incidence and morbidity of wasting associated with cancer. Studies intended to evaluate new therapies should include the following:

1. Measurements of weight, height, mid arm circumference and body mass index
2. A functional assessment- self reported and observed
3. Life perception assessment- self reported and consistently administered
4. Be controlled for concomitant medications
5. If body composition is measured, more than one modality should be used to confirm interpretations of the observations
6. Duration of the treatment effect
7. Follow up analysis for survival

LITERATURE CITED


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<th>TABLE 1</th>
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<tbody>
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<td><strong>Low Tech</strong>-available in a normal clinic or office</td>
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<tr>
<td><strong>Mid Tech</strong>-available at a specialty clinic or referral center</td>
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<tr>
<td><strong>Tertiary Care Center</strong></td>
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<td><strong>High tech</strong>-Research Center</td>
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| **Observation during meals, food diary** |
| **Height, weight, and calculation of body mass index = (weight in kg)/(height in m)^2** |
| **Anthropometry, bioelectric impedance, densitometry** |
| **Performance status, functional tests, time to recovery from previous therapy** |
| **Self assessment and administered questionnaires** |

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<th>TABLE 2</th>
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<td><strong>Question—Is there a change in</strong></td>
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<td><strong>Assessment</strong></td>
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<td>intake?</td>
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