Phase Angle as a Prognostic Indicator in Cancer

Henry C. Lukaski[a,b] and Michaeal G. Singer[b]

[a]Department of Internal Medicine, School of Medicine and Biomedical Sciences,
University of North Dakota, Grand Forks, ND 58202 (henry.lukaski@und.edu) and
[b]IPGDx, Harrisville, MI 48740 (michaealsinger@ipgdx.com)

Abstract

Current methods to evaluate the severity and progression of the disease, effectiveness of therapy and survival among cancer patients are generally limited in their prognostic ability. Whole-body phase angle, measured by using a tetrapolar, phase-sensitive bioelectrical impedance analyzer, offers a new approach. Phase angle (arc tangent of the ratio of reactance to resistance) is a non-invasive measurement of tissue bioelectrical properties. Findings from observational studies reveal that phase angle is an independent indicator of prognosis in cancer because it illustrates cell membrane integrity and function that are not possible with other measurement approaches. We propose a phase angle-based biometric scoring system for prognosis in cancer. Phase angle measurements outside the range of normal values indicate categorical states (frailty and morbidity) with the severity based on magnitude and rate of diminution of the phase angle value compared to the early diagnosis value. Change in the rate of ascent, plateau and decline of the phase angle indicate impact of therapy throughout the clinical intervention and may provide significant additional prognostic information in support of improved decision making. Thus, phase angle immediately offers a safe, practical, economical, FDA-approved device and a unique biometric scoring system into the clinical practice of cancer treatment.

Introduction

Cancer is the second leading cause of death in the United States and responsible for more that 560,000 deaths in 2010 (ACS 2010). Although advances in diagnosis and treatment of cancer continue to improve the 5-year survival rates for all cancers, the need persists for better methods, individually or in concert with existing approaches, to evaluate and modify treatment, and further increase survival. In addition, objective biomarkers that predict non-acute death in cancer are needed.

Prognosis, characterized as the usual course of a disease, is an uncertain process that integrates clinical data derived from biomedical tests and physician experience to predict possible future outcomes of a treatment for an individual with cancer. Physician accuracy of prognosis is limited and statistically based methods are too imprecise for individual patient use, and accuracy at present is limited to the last 30 days of life when the potential for positive impact is significantly reduced (Christakis and Lamont 2000). Prognosis includes an assessment of the presence and severity of disease, the effectiveness of treatment, frailty or vitality, and timing of non-acute death in chronic disease. Current laboratory measures, molecular and genetic markers, radiological imaging studies, and physical examination are generally limited in their prognostic abilities (Ludwig and Weinstein 2005; Chang et al. 2006; Stockler et al. 2006; van der Schroeff et al. 2010). Similarly, prognostication in palliative care is often inaccurate with errors systematically optimistic resulting in an increased burden on patients and families (Christakis and Lamont 2000; Glare and Sinclair 2008; Higginson and Costantini 2002). Therefore, an imminent need exists for a more accurate and reliable approach to supplement currently used measurements in the prognosis of cancer patients and end of life decision making.

Bioelectrical Phase Angle

Living organisms consist of conductive and non-conductive components with fluid volumes, tissue properties and cell membranes as the primary electrically recognized constituents (Foster and Lukaski 1996). When an organism becomes a component of a safe and highly controlled electrical circuit, the measured change or decrease in voltage following the administration of a safe, radiofrequency, alternating current yields bioelectrical measurements that designate structural and functional biological variables. Resistance is the opposition to the applied current and is inversely proportional to extracellular fluid vol-

ume. Reactance represents the delay in the conduction of the administered current by cell membranes. Capacitance, due to membrane structure and function, causes the current to lag behind the voltage creating a phase shift that is quantified as the angular transformation of the ratio of reactance to resistance (arc tangent of reactance/resistance times 180°, divided by π and expressed in degrees) or phase angle. A phase-sensitive impedance analyzer administers the constant current at a fixed frequency into the bioelectrical circuit and measures the voltage drop that results from the inclusion of the body within the circuit.

A critical aspect of phase angle determination is the requirement to use a phase-sensitive device. Because phase angle consists of two components, reactance and resistance, a bioimpedance analyzer must determine reactance and resistance directly and accurately. Experimental findings emphasize significant errors in determination of reactance (10 to 12 ohm) and resistance (5 ohm) with impedance devices that do not directly determine reactance *in vivo* (Lukaski 2009). This magnitude of error can introduce uncertainty of 15 to 20% in reported reactance data and result in inaccurate and variable (non-systematic error) phase angle values up to 1°. Furthermore, quality control data determined with a phase-sensitive impedance analyzer demonstrate *in vivo* test re-test reliability for reactance and resistance measurements is very high (0.98 to 0.99) with *in vivo* precision for within-day and between-day measurements should be <1.5% and <2%, respectively, for reliable phase angle determinations (Lukaski 2009).

Phase Angle in Cancer Prognosis

Phase angle provides a unique view into the hierarchy of physiology based on the concept that the body consists of successive, dependent and complex components that may be examined in the development of a prognosis for an individual. Holistically, biomolecules, microscopic structures, organelles, cells, tissues, organs, and systems compose the body; the structure or function of one or a combination of the components can be determined and compiled to formulate a prognosis. Traditional laboratory tests (cells counts, chemistries, genetic markers, etc), imaging techniques (CT and MRI) and physical examination encompass cells, tissues, organs, and systems. In contrast, phase angle characterizes bioelectrical correlates of cell membrane function that enables earlier insight into disturbances of health and responses (positive or negative) to pharmacological and other interventions compared to the other levels of testing.

Disease, inflammation, infection, malnutrition or prolonged physical inactivity can result in disturbed electrical properties of tissues that directly affect the phase angle. Awareness of the importance of phase angle as a prognostic indicator in advanced cancer is growing because of its ability to non-invasively ascertain tissue bioelectrical properties and the lack of reliance on assumptions of constant chemical composition of the fat-free body. Phase angle directly relates to cell mass and function and thus indexes cell vitality (Norman et al. 2010). Accumulating evidence supports phase angle as a practical indicator of survival among cancer patients. Observational and prospective studies report that a decreased phase angle value is a significant and independent predictor of prognosis in many types of advanced cancer (Toso et al. 2000; Gupta et al. 2004a, 2004b, 2008, 2009; Norman et al. 2010; Paiva et al. 2011). These descriptive findings support that phase angle is a unique biomarker of functional mass, which is known to decrease in patients with advanced cancer. However, markedly decreased nutritional status, evidenced as significant reduction in body cell mass, occur relatively late in most cancer conditions. Because phase angle is sensitive to alterations in tissue electrical properties, early disturbances in cell membrane function can be identified by longitudinal decreases in phase angle values that reflect altered cell function that precede diminution of body cell mass.

A novel application of phase angle is routine assessment of the impact of therapy on prognosis in patients with cancer. This application arises from observations that, in response to pathology or therapy, changes in phase angle precede somatic or traditional biochemical responses. We developed a biometric scoring system for patient assessment (PrognostiCheck®) that is based on three issued US Patents (6587715, 7003346 & 7136697). This scoring system requires a phase-sensitive impedance instrument and utilizes only measured resistance, reactance and phase angle, without reliance on prediction models or assumptions related to body composition, for estimation of prognosis (presence, progression and severity of disease; effectiveness of treatment and timing of non-acute death) in any biological entity. This clinical application uses categorical ranges of phase angle that correspond to indices of quality and function of body cells, as well as body cell mass. The average range of phase angle in healthy humans is 5 to 9°, and depends on age, gender and body mass index (Bosy-Westphal et al. 2006; Norman et al. 2010; Paiva et al 2011). For an individual, greater phase angle values are associated health and vitality (such as muscle strength, respiratory function, and quality of life). In contrast, lesser phase angle values, expressed either as <5th percentile of reference population data or <2°, are indicative of illness and frailty or decreased survival rate.

Categorical ranges of phase angle may be implemented in prognosis for individual patients. Phase angle values less than 5° indicate significant frailty. Lesser values, 4 to 2°, signal a serious condition with the need for aggressive intervention whereas phase angle values of 2° or less indicate impending death. Serial, longitudinal measurements provide estimates of rate of change in health status and

serve as a biomarker to monitor the course of a disease (improvement or deterioration) and the need for change of treatment intervention. In a patient under observation, the decline of 1° in phase angle indicates disease compromise with the rate of diminution directly related to the severity of the condition. For example, phase angle values fall rapidly with an escalation in infective processes and multisystem organ failure. In contrast, attenuation in the decline in phase angle values is seen in patients with chronic neurodegenerative processes such as ALS or Alzheimer's. Thus, serial tracking of longitudinal phase angle measures illustrates the trajectory of the condition at hand. More frequent phase angle measurements are made in accelerated conditions or during therapeutic interventions to assess treatment effectiveness as a slowed diminution or plateau of the measured phase angle value that illustrates improvement; in contrast, a rapid descent signals unresponsive and unrecoverable conditions. Recent evidence indicates that phase angle is an early and independent indicator of benefit of intervention. Among patients with advanced pancreatic cancer, phase angle increased significantly in response to parenteral nutrition and was a better prognostic indicator of improved nutritional status than body weight (Pelzer et al. 2010). Thus, phase angle data provide a valuable new dimension to the clinical decision matrix and are readily utilized to support compliance, communication and the assessment of benefit versus burden particularly at transition from curative or restorative to palliative or hospice care.

Conclusion

Phase angle is a global indicator of the condition of an individual cancer patient; it encompasses the effects of cancer and cumulative treatments on tissue bioelectrical characteristics. Phase angle differs from currently used prognostic indicators such as tumor staging that describes the anatomical extent of the cancer disease process, and molecular and genomic approaches that assess risk and treatment response potential. It offers novel information and value to the clinical decision-making matrix and supports the assessment of benefit versus burden in discussions related to end of life decisions with patients and families dealing with cancer. Thus, phase angle provides a clinically feasible index to guide the decision process of physicians, patients and families alike.

References

American Cancer Society. Cancer Facts and Figures 2010. Atlanta, GA: American Cancer Society.

Christakis, N. A. and Lamont, E. B. 2000. Extent and Determinants of Error in Doctor's Prognoses in Terminally Ill Patients: Prospective Cohort Studies. British Medical Journal 320:469-473.

Ludwig, J. A. and Weinstein, J. N. 2005. Biomarkers in Cancer Staging, Prognosis and Treatment Selection. Nature Reviews Cancer 5:845-856.

Chang, L., Horng, C.-F., Huang, Y.-C. T., and Hsieh, Y.-Y. 2006. Prognostic Accuracy of Acute Physiology and Chronic Health Evaluation II Scores in Critically Ill Cancer Patients. American Journal of Critical Care 15:47-53.

Stockler, M. R., Tattersall, M. H. N., Boyer, M. J., Clarke, S. J., Beale, P. J., and Simes, R. J. 2006. Disarming the Guraded Prognosis: Predicting Survival in Newly Referred Patients with Incurable Cancer. British Journal of Cancer 94:2008-212.

van der Schroeff, M. P., van Schie, K., Langeveld, T. P. M., Looman, C., and de Jong, R. J. B. 2010. Model-Assisted Predictions on Prognosis in HNSCC: Do We Learn? European Archives of Otorhinolaryngology 267:1445-1448.

Glare, P. A. and Sinclair, C. T. 2008. Palliative Medicine Review: Prognostication. Journal of Palliative Medicine 11:84-93.

Higginson, I. J. and Constantini, M. 2002. Accuracy of Prognosis Estimates by Four Palliative Care Teams: a Prospective Cohort Study. BMC Palliative Care 1:1.

Foster, K. R. and Lukaski, H. C. 1996. Whole-Body Impedance – What Does It Measure? American Journal of Clinical Nutrition 64:388S-396S.

Lukaski, H. C. 2009. Evaluation of Body Composition: Why and How? Mediterranean Journal of Nutrition and Metabolism 2:1-10.

Norman, K., Stobaus, N., Zocher, D., Bosy-Westphal, A., Szramke, A., Scheufele, R., Smoliner, C., and Pirlich, M. 2010. Cutoff Percentiles of Bioelectrical Phase Angle Predict Functionality, Quality of Life, and Mortality in Patients with Cancer. American Journal of Clinical Nutrition 92:612-619.

Toso, S., Piccoli, A., Gusella, M., Menon, D., Bononi, A., Crepaldi, G, and Ferrazzi, E. 2000. Altered Tissue Electrical Properties in Lung Cancer Patients as Detected by Bioelectrical Impedance Vector Analysis. Nutrition 16:120-124.

Gupta, D., Lammersfeld, C. A., Burrows, J. L., Dahlk, S. L., Vashi, P. G., Grutsch, J. F., Hoffman, S., and Lis, C. G. 2004a. Bioelectrical Impedance Phase Angle in Clinical Practice: Implications for Prognosis in Advanced Colorectal Cancer. American Journal of Clinical Nutrition 80:1634-1638.

Gupta, D., Lis, C. G., Dahlk, S. L., Vashi, P. G., Grutsch, J. F., and Lammersfeld C. A. 2004a. Bioelectrical Impedance Phase Angle as a Prognostic Indicator in Advanced Pancreatic Cancer. British Journal of Nutrition 92:957-962.

Gupta, D., Lammersfeld, C. A., Vashi, P. G., King, J., Dahlk, S. L., Grutsch, J. F., and Lis, C. G. 2008. Bioelectrical Impedance Phase Angle as a Prognostic Indicator in Breast Cancer. BMC Cancer 8:249.

Gupta, D., Lammersfeld, C. A., Vashi, P. G., King, J., Dahlk, S. L., Grutsch, J. F., and Lis, C. G. 2009. Bioelectrical Impedance Phase Angle in Clinical Practice: Implications for Prognosis in Stage IIIB and IV Non-Small Cell Lung Cancer. BMC Cancer 9:37.

Paiva, S. I., Borges, L. R., Halpern-Silveira, D., Assuncao, C. F., Barros, A. J. D., and Gonzalez, M. C. 2011. Standardized Phase Angle from Bioelectrical Impedance Analysis as Prognostic Factor for Survival in Patients with Cancer. Support Care Cancer 19:187-192.

Bosy-Westphal, A., Danielzik, S., Dorhofer, R.-P., Later, W., Wiese, S., and Muller, M. J. 2006. Phase Angle from Bioelectrical Impedance Analysis: Population Reference Values by Age, Sex, and Body Mass Index. Journal of Parenteral and Enteral Nutrition 30:309-316.

Pelzer, W., Arnold, D., Goevercin, M., Stieler, J., Doerken, B., Riess, H., and Oettle H. 2010. Parenteral Nutrition Support for Patients with Pancreatic Cancer. Results of a Phase II Study. BMC Cancer 10:86.