

Entering a New Era in the Management of Tumor-associated Involution

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Commentary on "Are Inflammatory Cytokines the Common Link Between Cancer-associated Cachexia and Depression?" by James Illman, BS, Robert Corringham, MD, Don Robinson, Jr, MSPH, et al (page 37).

Often, a clinician can feel it in his or her bones long before a mechanism explaining associated phenomena has been developed. For generations, physicians and nurses caring for patients with cancer have been aware that cachexia, depression (that can precede the diagnosis of cancer), and debilitation frequently occur in association in patients with cancer. The empiric observation that these complications are tightly associated and occur in certain clinical situations (eg, lymphomas; bronchogenic, pancreatic, or renal cell cancers; any cancer metastatic to the liver; whole brain irradiation) long ago led to the hypothesis that these systemic manifestations are caused by factors either elaborated by the tumor or produced by the body in response to cancer. This hypothesis actually predated the appearance of the word "cytokine" in the medical literature. And there the concept lay, widely accepted as intuitively obvious to anyone with bedside smarts and frustratingly beyond a mechanistic understanding that could support a rational therapeutic approach.

The introduction of cloned immunomodulatory proteins into cancer clinical trials was the watershed in our understanding of the biology of tumor-associated involution. It brought the word "cytokine" into our vocabulary. But much more importantly, the administration of these agents, most famously type 1 interferons and interleukin-2 (IL-2), produced clinical syndromes in patients that rapidly and unmistakably mimicked "wild type" cancer involution in patients who had been

asymptomatic. Most surprising was the effect of these agents on mental function and their ability to induce severe depression, even in patients without detectable cancer who were receiving adjuvant therapy. Parenthetically, one of these cytokines had been isolated as a potential cause of cachexia and was briefly named cachectin, before its immunomodulatory and possible antitumor effects were recognized, and it was more optimistically, but perhaps less appropriately, renamed tumor necrosis factor (TNF). We had an epiphany; cytokines elaborated as part of a systemic antitumor response were responsible for the cancer involution syndrome. Finally, the recent discovery that inflammation causes anemia and that anemia further worsens cytokine-mediated fatigue and depression brought us to our current simplistic working model (Figure 1).

But what cytokines are the most important in driving the tumor-associated involution that is so devastating to the quality of life of patients with cancer and often limits their survival? Illman and his colleagues have done an excellent job of summarizing the bewildering literature linking cachexia and depression to a recurring list of suspects: TNF- α , interferon-alpha (IFN- α), IL-6, transforming growth factor-beta (TGF- β), IL-1 β , IL-2, and, less frequently, IL-8 and IL-12. These authors also correctly point out that very selective TNF and IL-1 blockers are available for clinical use in patients with rheumatologic disorders and that novel, broader spectrum anti-inflammatory molecules, such as thalidomide (Thalomid) and its analogs, are in clinical use in cancer therapy. So we have new and powerful tools and some rudimentary molecular understanding of the pathophysiology of the problem to go with them; dare we speak the well-worn mantra of "translational research" leading to "targeted therapies"?

Challenges to Be Faced

Working out the successful management of cytokines to minimize depression, cachexia, and

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J Support Oncol 2005;3:051-052

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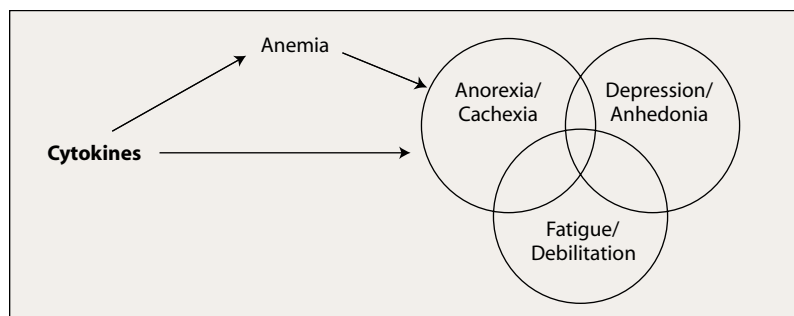


Figure 1 Schema of Relationship Among Cytokines, Anemia, Cachexia, and Depression

Cytokines, Cachexia, and Depression

fatigue is likely to be difficult, with several obvious challenges that will inevitably lead to some disappointments:

- We do not have reliable and validated measures of the level of activity of a particular cytokine in a given patient, let alone the ability to determine whether that cytokine is requisite to that patient’s symptoms. Serum levels are inadequate for this purpose, with significant fluctuations over time and poor correlations with symptoms. For instance, we may learn that a small number of patients benefit from a given intervention but may be unable to predict who those patients will be.

- The immunocytokine system is complicated, with cytokines regulating the activity of other cytokines and high degrees of amplification and built-in redundancy that may sabotage strategies based upon precise targeting of one cytokine or receptor. Moreover, it is not uncommon in immunocytokine clinical research for one dose of a cytokine to improve a condition and a higher dose to have the opposite effect; choosing the right dose of the right cytokine blocker will require meticulous dose finding.

- The number of agents available for testing is large and growing, with a staggering number of possible combinations, any one of which might be the Holy Grail but all of which cannot be sys-

tematically tested, at least in the remaining lifetime of current investigators who would like to see this problem solved.

- Safety inevitably will be an issue. Some of the agents mentioned by the authors have been implicated in increasing the incidence of lymphomas, are known to be highly teratogenic, or may block tumor cell apoptosis, and there will be the overarching concern regarding any immunosuppressive therapy in patients with cancer. Clinical trials will need to incorporate controls and robust safety analyses.

- The application of agents with broad activity against the inflammatory cascade, such as corticosteroids or non-steroidal anti-inflammatory agents, to the cancer-cachexia syndrome has produced occasional successes but overall disappointing results. And when the cancer-cachexia syndrome is caused by cytokine therapy, it does not improve until weeks or months following discontinuation of that therapy. The syndrome does not break easily or rapidly.

Notwithstanding, it is clear that we are entering a new era in the management of tumor-associated involution, and there are reasons for optimism regarding ultimate success. We have excellent tools to reliably measure fatigue and depression as outcomes in clinical trials. We have promising new drugs and the beginnings of insight into how they may work to relieve this syndrome. We have powerful new approaches, such as pharmacogenomics and pharmacoproteomics, which will provide better insight into the biology and a way to choose the most promising approaches to test. The remarkable success of erythropoietic agents, which address only a portion of the fatigue suffered by these patients, will make cracking the larger involution syndrome one of the most attractive opportunities to make a valuable difference for patients—and should assure adequate resources to support a sustained research effort. A quantum advance in the care of patients with this syndrome is coming. I can feel it in my bones.