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Review in Depth

Incorporating Biomarkers of Frailty and Senescence in Cancer Therapeutic Trials

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Abstract
As the population ages, oncologists are faced with the quandary of how to efficiently identify frail individuals that may have more difficulty tolerating and recovering from systemic therapy for cancer. Recent advances have been made in recognizing frailty via clinical geriatric assessment of older patients with cancer. These advances appear to allow for better prediction of toxicity than physician-rated performance status. Although the development of these tools is a large step forward in geriatric oncology, we still lack an understanding of how the underlying biologic processes of aging affect tolerance of cancer treatment. Determining specific biologic causes underlying frailty may allow oncologists to become even more adept at identifying patients at risk for excessive toxicity and provide the opportunity to therapeutically target these processes to help improve tolerability and survival outcomes for older patients with cancer. This article provides a background on potential biologic factors that may identify frail individuals at increased risk for toxicity related to cancer treatment. Potential methods to incorporate these factors into cancer therapeutic trials are discussed.

Key Words: Geriatric oncology—Frailty—Biomarkers of frailty.

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The incidence and prevalence of cancer among older adults will increase dramatically over the next 30 years in large part because an elderly population is growing in the United States and other parts of the world. It is estimated that 70% of cancers will occur in patients older than 65 years by the year 2030 (1). The complexities of treating older cancer patients have begun and will continue to pose a great challenge to the oncologic community. One of the greatest difficulties in treating older adults with cancer is finding the right balance between providing effective cancer therapy and minimizing treatment-related toxicity (2).

Concern for poor treatment tolerance partially explains why older adults with cancer are undertreated and underrepresented in clinical trials (3,4). Surveyed oncologists cited treatment toxicity as a major challenge when caring for older adult cancer patients (5). Toxicity risk is also considered a substantial barrier to clinical trial enrollment (6). As a result, we lack an understanding of how to apply new standards of cancer care to the older adult population, and these patients do not appear to consistently gain the survival benefits of cancer therapeutic advances as much as younger patients (7,8).

The decision to treat older adults with cancer should not be based on chronologic age alone, since there is great variability in health among older patients. Indeed, some older cancer patients can derive similar benefit from treatment as younger patients without excessive toxicity (9–12). One way to predict a patient’s tolerance to cancer therapy is to assess degree of frailty, or in essence, “biologic age” (13,14). The GA tool that is recommended for all geriatric oncology patients (15).

The GA is the best tool currently available to determine a patient’s degree of frailty, but it does not appear to be gaining widespread use
Frailty

The aging continuum ranges from healthy, well-functioning individuals to those who are disabled. At some point during aging individuals develop frailty, which is a physiologic process associated with less functional reserve to compensate for internal and external stress to the body predisposing patients to rapid deterioration of health and functional decline (17–19). As frailty progresses, the aging process accelerates; patients have less physiologic reserve and become more vulnerable to disability (Figure 1). Frailty is not synonymous with disability (limited ability for self care) or comorbidity (burden of coexisting medical illnesses) (20). Rather, comorbidity is a risk factor for frailty and disability is a result of frailty.

Despite their vulnerability, frail patients may not have readily apparent signs indicating that they are at risk for adverse events from cancer treatment, and this is exactly the challenge many oncologists face as they try to determine how a particular older patient will respond to systemic chemotherapy. A patient sitting in the exam room may appear well at rest, and a patient's limited organ reserve may not be apparent until the patient is stressed by systemic chemotherapy.

This point is illustrated by the recent clinical trial N0147, which randomized patients with resected stage III colon cancer to receive adjuvant chemotherapy plus the biologic agent cetuximab, an epidermal growth factor receptor antibody, versus chemotherapy alone (control arm) (21). Of the 1,861 patients with KRAS wild-type colon cancer enrolled on the trial, 259 patients were more than or equal to 70 years. Unexpectedly, elderly patients in the experimental arm had significantly decreased overall survival at 3 years compared with the control arm, 72.5% and 86.2%, respectively ($p = .03$), whereas no survival difference was seen between arms in younger patients. The decreased survival among elderly patients may be explained by significantly higher incidence of grade 3 or higher toxicity compared with patients younger than 70 (81% vs 72%; $p = .02$) resulting in $20\%$ fewer elderly patients completing the recommended adjuvant treatment and only $57.5\%$ of elderly patients receiving the planned chemotherapy dose (vs $80\%$ in younger patients). No clinical characteristics, other than age, were found that predicted toxicity specifically for elderly patients (22).

The results of the N0147 trial highlight that even among good performance status patients apparently healthy enough to be enrolled in a clinical trial, there is something unrecognized about the biologic process of aging that predisposes older patients to higher toxicity rates. It also highlights the need for better frailty assessment of geriatric patients. It is likely that some of the older patients enrolled in N0147 had greater degrees of frailty and less functional reserve to withstand the stress of systemic therapy, which resulted in higher rates and greater severity of adverse effects.

Recognizing Frailty in Cancer Patients

The “frailty phenotype” is comprised of eight domains addressed in most geriatric assessments: mobility, strength, balance, motor processing, cognition, nutrition, endurance, and physical activity (23). These domains are tested in the comprehensive GA, which has been shown to predict toxicity, morbidity and mortality in the oncologic population (14,24). A number of factors, including labor intensity, poor reimbursement, and lack of geriatric-trained staff, limits incorporation of frailty testing into routine clinical practice (16).

Recognizing this burden, investigators have devised screening methods to identify those older patients who would benefit most from GA, but still a large percentage (70%) of patients required GA (25). The less-extensive, cancer-specific geriatric assessment (CSGA) contains items mostly completed by the patient, taking an average 27 min for the patient to complete (26). When used prospectively in a clinical trial, the CSGA was better able to predict toxicity than the physician-assessed Karnofsky Performance Status (27). The results from incorporating the CSGA highlight that this degree of assessment provides additional, complementary information on vulnerability (or frailty) beyond what is recognized by the physician in a routine office visit. It also highlights the need for better screening to determine which older patients are at risk. However, it is unclear if the CSGA can identify pre-frail patients without obvious functional deficits.

The Biologic Basis of Frailty

Frailty is thought to have a biologic basis that is loosely correlated with chronologic age (Figure 1) (28). Although the underlying physiologic mechanisms of frailty remain unclear, multiple studies suggest

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Figure 1. The Aging Continuum
Table 1. Biomarkers Associated With Frailty, Functional Decline, or Mortality

<table>
<thead>
<tr>
<th>Reference</th>
<th>Biomarkers Tested</th>
<th>Association</th>
<th>Measures</th>
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<tbody>
<tr>
<td>Ronning et al. (39)</td>
<td>CRP, IL-6, TNF-α, D-dimer</td>
<td>Frailty</td>
<td>Comprehensive Geriatric Assessment</td>
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<tr>
<td>Walston et al. (40)</td>
<td>CRP, fibrinogen, factor VIII, and D-dimer</td>
<td>Frailty</td>
<td>Fried frailty phenotype (65)</td>
</tr>
<tr>
<td>Hubbard et al. (37)</td>
<td>CRP, IL-6, TNF-α, albumin</td>
<td>Frailty</td>
<td>Fried frailty phenotype (65); Rockwood Frailty Index 66</td>
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<tr>
<td>Leng et al. (38)</td>
<td>IL-6, WBC</td>
<td>Frailty</td>
<td>Fried frailty phenotype (65) Walking speed, chair-stand test, standing balance test and hand-grip strength</td>
</tr>
<tr>
<td>Cesari et al. (36)</td>
<td>CRP, IL-6, and IL1RA</td>
<td>Frailty</td>
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<td>Ferrucci et al. (45)</td>
<td>IL-6</td>
<td>Functional decline</td>
<td>Self-report of functional status, objective measures of walking performance, and knee extensor strength</td>
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<td>de Saint-Hubert et al. (43)</td>
<td>IL-6, IGF-1</td>
<td>Functional decline</td>
<td>Score Hospitalier d’Evaluation du Risque de Perte d’Autonomie (SHERPA) (predictive tool for functional decline) (67)</td>
</tr>
<tr>
<td>Puts et al. (41)</td>
<td>CRP, 25(OH)D, IL-6, IGF-1</td>
<td>Functional decline [25(OH)D, CRP]</td>
<td>Frailty defined as presence of three out of nine frailty indicators 3- and 7-year mortality and Rosow–Breslau Functional Decline scale (68)</td>
</tr>
<tr>
<td>Reuben et al. (47)</td>
<td>Albumin, low cholesterol, IL-6, CRP</td>
<td>Mortality</td>
<td>Katz and Akpom (69), Nagi (70), Rosow and Breslau (68), instrumental activies of daily living.</td>
</tr>
<tr>
<td>Cohen et al. (42)</td>
<td>IL-6, D-dimer</td>
<td>Functional decline and mortality</td>
<td>Katz and Akpom (69), Nagi (70), Rosow and Breslau (68)</td>
</tr>
<tr>
<td>Huffman et al. (46)</td>
<td>s-Vascular cell adhesion molecule</td>
<td>Frailty and mortality</td>
<td></td>
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</table>

A state of increased inflammation with secondary changes in coagulation exists in frail individuals. There is a spectrum of proinflammatory and coagulation mediator levels in the serum, such as IL-6 and TNF-α D-dimer, and plasminogen activator inhibitor-1, which increase as people age, that are felt to exacerbate multiple age-related diseases and to accelerate the aging process (29–35). Table 1 includes a list of studies investigating inflammatory and/or coagulation proteins as they relate to higher degrees of frailty, functional decline, and mortality in the general geriatric population.

Across differing measures of frailty, levels of proinflammatory cytokines and coagulation factors including C-reactive protein (CRP), IL-6, and TNF-α, D-dimer, and soluble vascular cell adhesion molecule (s-VCAM) are higher in frail patients, compared with age-matched nonfrail controls in the general geriatric population (36–41). A recent study of 110 patients over 75 years evaluated the relationship between frailty measures and TNF-α, IL-6, CRP, and low albumin (37). Increasing frailty scores were significantly correlated with higher inflammatory marker levels and lower albumin levels even after adjusting for multiple factors including age, sex, body mass index category, smoking status, number of comorbidities and number of prescribed medications.

Elevated chronic inflammatory and procoagulant markers can predict functional decline (41–45). Ferrucci and coworkers (45) found that women with elevated IL-6 levels at baseline had significantly higher levels of functional decline including decreased mobility, activities of daily living deficits; increased walking limitations; and decreased walking speed, compared with women with low IL-6 levels. Increased levels of inflammatory cytokines and procoagulant markers also correlate with functional decline after hospitalization and postoperative complications after oncologic surgery (39,43).

Markers of chronic inflammation and coagulation are associated with all-cause mortality risk in the elderly people (42,46,47). The ability of these markers to predict mortality was demonstrated in a population of community dwelling adults (mean age 78). s-VCAM was independently related to poorer functional status at baseline and independently related to 4-year mortality (Hazard ratio 1.2, \( p = .002 \)) (46). After functional status, demographic factors, and comorbidities were taken into account, s-VCAM, D-dimer, and IL-6 concentrations were independently related to mortality within 4 years. Remarkably, a single standard deviation increase in the log of s-VCAM concentration at baseline was associated with a 2.75-fold increase in mortality.

The processes resulting in an increase in proinflammatory cytokines and elevated procoagulant markers are interrelated. Inflammatory cytokines such as TNF-α and IL-6 stimulate production of prothrombotic factors such as plasminogen activator inhibitor-1 (an inhibitor of fibrinolytic activity) and fibrinogen (33). In turn, D-dimer, a marker of the clotting process, has been shown to induce synthesis and release of cytokines IL-1β, IL-6, and plasminogen activator inhibitor-1 (48). Another example is when VCAM is exposed to TNF-α and IL-1β, it is cleaved to soluble (s)-VCAM, s-VCAM is a measure of endothelial dysfunction associated with many age-related diseases including metastatic malignancies (49).

**Etiology of Inflammatory/Coagulation markers**

Although chronic inflammatory markers and procoagulant factors are associated with frailty, the underlying mechanisms leading to an increase of these factors as people age remains to be elucidated. Potential etiologies include acute or chronic illnesses, the increasing burden of tissue damage, alterations in the innate and adaptive immune system, or the deterioration of homeostatic repair mechanisms (20,34). A broadening area of research relevant to the basic science of aging suggests cellular senescence may be an underlying mechanism contributing to increased levels of serum inflammatory and coagulation mediators associated with aging and frailty.
Cellular senescence is the term used to describe the cessation of haploid cell division. Cellular senescence can be a result of a high number of prior cell division and telomere shortening, termed replicative senescence, or as a result of cellular stress such as toxins, irradiation, or oncogene activation (50). This mechanism is felt to be protective against the development of cancer in younger years, but senescent cells may have detrimental effects as these cells accumulate in tissues with age (51,52). Although senescent cells no longer retain their mitotic activity, they remain viable, with changes in gene expression resulting in production of proinflammatory proteins referred to as the senescence-associated secretory phenotype (SASP) (53). These factors may contribute to increased inflammation in surrounding tissues and in the circulation, which has been theorized to contribute to the aging process. Indeed, factors comprising the SASP are very similar to the inflammatory and coagulation markers that are associated with frailty and mortality in the elderly (30,54).

While the direct link with cellular senescence and the aging process has not been definitely established, research with progeroid mouse models demonstrated expression of SASP components such as IL-6, insulin-like growth factor-binding protein-2, and plasminogen activator inhibitor-1 are higher in senescent cells in fat tissue than in non-senescent cells in the same tissue (55). In addition, clearance of senescent cells in these mouse models reduced expression of SASP factors in fat and skeletal muscle tissue and delayed the onset of the mouse aging phenotype. Whether reducing senescent cell burden would also reduce circulating inflammatory factors remains unknown.

Potential circulating markers associated with cellular senescent cell burden have been identified, including high-mobility group box protein-1 and Wnt16, which could be measured in the serum. If senescent cells contribute to the inflammatory and coagulation proteins associated with frailty, then measuring circulating indicators of senescent cell burden may also be a method to identify those elderly patients who are at risk from adverse outcomes from cancer treatment. In addition, any future therapeutic agents that target senescence may have the potential to decrease the amount of circulating inflammatory and procoagulant markers and potentially impact the degree of frailty.

The data compiled in this review suggests there is an association between markers of inflammation/coagulation and frailty in the aging process. Because frail patients have low functional reserve to withstand a physiologic stress to the body, it stands to reason that these frailty markers could identify patients at increased risk for toxicity and poorer survival. The associations of these markers with frailty, functional decline, and mortality are independent of age, comorbidity, and functional status (42,43–47,49,56). Therefore, these markers may identify prefrail and frail patients that may not otherwise be identified in a routine office visit and may augment the screening older patients with cancer prior to initiating treatment.

Mediators of cellular senescence, such as telomere shortening and DNA damage, are potential biomarkers of aging (57). A few studies have shown an association with shortened telomere length and mortality (58,59), but evidence to suggest a relationship between telomere length and physical function and/or frailty is lacking (60). p16INK4a is a marker of DNA damage response and another promising biomarker of aging. Not only has p16INK4a been shown to increase with age in mammalian models and humans but also its expression has been correlated with higher levels of IL-6, considered a marker of frailty (61,62). Studies evaluating p16 levels in the geriatric oncology population are ongoing (http://www.clinicaltrials.gov/ct2/results?term=NCT00849758).

There are many unknowns regarding the etiology and impact of these markers on cancer treatment tolerance and survival outcomes. The role of cellular senescence in the development of frailty is not well studied, but the preclinical evidence of the association with frailty is intriguing. Although it is recognized that the underlying biologic mechanisms remain to be elucidated, it is plausible these markers could be considered hallmarks of the mechanisms, and therefore frailty, regardless of their etiology. Therefore, studies are warranted to assess for a correlation of these markers with frailty and oncologic outcomes in relation to cancer treatment. For the purpose of the following discussion, the inflammatory, coagulation, and senescence markers discussed above will be referred to as biomarkers of frailty.

**Incorporating Biomarkers of Frailty Into Cancer Clinical Trials**

Prospective cancer clinical trials can be conducted to carefully and systematically address the unknowns of how the biologic effects associated with biologic age affect the tolerance of cancer treatment. Initially, frailty biomarker studies should be done in the adjuvant setting, where theoretically all disease has been removed to eliminate the potential confounder of the presence of cancer on levels of the markers and survival outcomes. If performed 6–8 weeks after surgery, the circulating acute phase reactants from the surgery itself should be resolved as well (63,64). Geriatric clinical trials have begun to incorporate systemic inflammatory markers into prospective clinical trials (www.clinicaltrials.gov/ct2/show/NCT01321658, www.clinicaltrials.gov/ct2/show/NCT00796978).

An example of how biomarkers of frailty can be included in geriatric oncology clinical trials is included in an trial in development investigating a novel agent for breast cancer entitled, Adjuvant Trastuzumab Emtansine (T-DM1) For Older Patients with Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer. The correlative biomarker studies aim to address the following questions:

1. **Do biomarkers of frailty in patients with cancer correspond to clinical measures of frailty?** Older patients with cancer would be assessed with clinical geriatric assessments at baseline, periodically throughout treatment, at the end of treatment, and 6 months after the completion of treatment. The relationship between the biomarkers and clinical levels of frailty will be assessed to determine if biomarker levels can reliably identify frail patients. The assessments throughout treatment will also provide information on the impact of chemotherapy on functional status and whether biomarkers not only correlate with the functional status assessment but also determine if they predict changes in function. Measurement 6 months after therapy will assess their clinical recovery and the long-term impact of cancer treatment on functional status.

2. **How does systemic cancer therapy affect circulating biomarkers of frailty?** Periodic measurements of biomarkers of frailty during cancer treatment can explore whether systemic therapy contributes to changes in acute or chronic inflammatory marker levels and changes in procoagulant marker levels. It will also determine whether exposure to systemic therapy increases the burden of senescent cells.

3. **Can elevated biomarkers of frailty predict which older cancer patients will have increased toxicity with cancer treatment?** During cancer treatment, data on toxicity are systematically collected via the Common Toxicity Criteria for Adverse Events method of grading and attribution of adverse events. The incidence of...
adverse events will be correlated with biomarkers of frailty to determine if there is an association with the biomarker levels and the incidence of toxicity with cancer treatment. Patients start with standard doses of adjuvant therapy when possible, and information on dose modifications and delays will be collected.

4. Do elevated biomarkers of frailty correlate with patient-reported outcomes such as quality of life, fatigue, and pain? With each evaluation, patient-reported outcomes will be collected. The relationship between biomarker levels and patient-reported outcomes will be analyzed to determine the relationship between biomarkers of frailty and overall patient well-being before, during, and after treatment.

5. Can biomarkers of frailty predict cancer-specific survival outcomes among cancer patients? Data on relapse-free, disease-free, and overall survival can be correlated with biomarkers of frailty to determine the prognostic ability of the biomarkers. In the older patient population, it is important to distinguish between deaths with and without recurrence of cancer because they are at higher risk for other competing causes of death.

Each analysis must carefully control for other potential confounding factors such as age, comorbidity, body mass index, antiinflammatory medications, cancer type and stage, and the specific cancer treatment. In addition, hemoglobin, creatinine clearance, and albumin have been found to be independent predictors of nonhematologic toxicity in the geriatric oncology population (15,27). These laboratory measures, which also give insight into functional reserve and cancer treatment toxicity risk, can be controlled for in correlative analyses.

Future studies could be done in the metastatic cancer setting to assess how cancer and age combined affect the levels of these markers, as well as the relationship of frailty markers to cancer treatment outcomes. One would expect increased tumor burden to correspond with elevated biomarkers of frailty. It would be interesting to explore if the circulating biomarker associated with the burden of cancer correlate with increased toxicity, and, if so, whether response to therapy would correspond with improvement of the biomarkers or a decrease toxic events.

**Potential Utility of Biomarkers of Frailty in Cancer Management**

If biomarkers of frailty are found to be predictive of toxicity, then they could be incorporated into prospective geriatric oncology trials to help determine clinical and biologic markers that have the greatest utility in predicting cancer treatment outcomes. Future studies will need to address how these frailty measures can be incorporated into clinical decision making to help guide clinicians on the most appropriate management of geriatric cancer patients. For instance, elevated biomarkers of frailty may give insight into whether dose modifications or less aggressive treatment regimens should be chosen. Conversely, if an older patient had very low frailty markers, this may increase the comfort level of a clinician to administer standard treatment. Potentially, such marker profiles could be incorporated into current geriatric assessment tools to enable cancer health care providers to be more accurate in assessing risk of adverse events outcomes in older cancer patients.

In addition to cancer treatment modifications, studying the interplay between the biology of aging and cancer will determine mechanisms underlying the physiology of frailty to provide rationale for future intervention studies to support frail patients during cancer treatment. For example, biomarkers of frailty may identify candidate interventions to improve physical function and potentially reduce the development of disability or loss of independence. Other interventions could include pharmacologic agents that reduce systemic inflammation or future agents that reduce senescent cell burden.

Biomarkers of frailty could be developed as an efficient and reliable screening tool for other disciplines where frailty is associated with the risk for poorer function and survival outcomes such as surgery, anesthesia, and radiation therapy in geriatric patients.

**Conclusions**

Multiple studies have demonstrated that markers of the activation of the chronic inflammatory and coagulation pathways are associated with frailty measures and predict functional decline and mortality in the general geriatric population. A spectrum of these markers among older individuals correlates with varying degrees of aging and physical performance. Biomarkers of frailty may be the ideal candidates to meet the needs of the geriatric oncology field where more tools are needed to accurately assess and accommodate the individual patient's level of frailty. These biomarkers may provide additional, complementary information about risk beyond what is identified on routine physician evaluation. Translational research on inflammatory, coagulation, and senescent markers in older adults could provide insight into the biologic basis of frailty and how it affects the tolerance of cancer therapy. In addition, gaining information on how biologic processes are affected by cancer treatment will pave the way for future interventional trials in geriatric oncology to guide treatment decisions and improve tolerance of therapy.

**References**


