The Lethal Phenotype of Cancer: The Molecular Basis of Death Due to Malignancy

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ABSTRACT The last decade has seen an explosion in knowledge of the molecular basis and treatment of cancer. The molecular events that define the lethal phenotype of various cancers—the genetic and cellular alterations that lead to a cancer with a poor or incurable prognosis—are being defined. While these studies describe the cellular events of the lethal phenotype of cancer in detail, how these events result in the common clinical syndromes that kill the majority of cancer patients is not well understood. It is clear that the central step that makes most cancers incurable is metastasis. Understanding the traits that a cancer acquires to successfully grow and metastasize to distant sites gives insight into how tumors produce multiple factors that result in multiple different clinical syndromes that are lethal for the patient. (CA Cancer J Clin 2007;57:225–241.) © American Cancer Society, Inc., 2007.

INTRODUCTION

In 2007, it is estimated that 559,650 people in the United States will die of cancer.1 The last decade has seen an explosion in the amount of knowledge in the molecular basis and treatment of cancer. Multiple studies have been published describing the molecular events that define the lethal phenotype of various cancers—the genetic and cellular alterations that lead to a cancer with a poor or incurable prognosis. While these studies describe the cellular events of the lethal phenotype of cancer in detail, how these events result in the common clinical syndromes that kill the majority of cancer patients is not well understood. The majority of solid-tumor malignancies kill patients because they escape the primary site and metastasize (Figure 1). The traits that a cancer acquires to successfully grow and metastasize to distant sites produce multiple factors that result in different clinical syndromes that are lethal for the patient.2–5 These syndromes can be broadly characterized into those related to cytokine overproduction and those related to organ failure. This paper describes how the molecular alterations of metastatic cancer result in the clinical lethal phenotype of cancer.

THE MOLECULAR BASIS OF CANCER

The process of carcinogenesis is the result of DNA damage that occurs in a normal cell and leads toward a growth and survival advantage (Figure 2).6–9 DNA damage is the result of gene–environment interactions on multiple levels, including the susceptibility for genetic damage inherited from parental genes.9,10 On their inherited genetic background, cells are assaulted by a variety of gene-damaging environmental agents, including radiation, viruses and other microbes, and chemical carcinogens, as well as the free radicals that are byproducts of normal cellular processes that accumulate with age. These DNA-damaging agents are modulated by host defenses and intrinsic organ- and extrinsic nonorgan–specific
risk modulators. Host defenses include the state of the patient’s immune system, nutritional status, and comorbid conditions. Intrinsic risk modulators are inherited traits that do not contribute directly to DNA damage, but modulate the environment that the cells are exposed to (ie, how well liver-metabolizing enzymes such as CYP3A function to modulate drug and hormone activity).  
Extrinsic risk modulators are best characterized by chemoprevention agents (ie, antioxidants such as selenium and vitamin E that remove damaging oxygen radicals from the intracellular environment by facilitating their breakdown to water).  

Regardless of how damage to the genome originates, cancers are the result of mutations that result in a group of common characteristics or “hallmarks” that define the minimum set of survival traits that a cancer cell must acquire to flourish (Figure 1). These hallmarks include the following: (1) genetic instability; (2) limitless replicative potential (immortality); (3) anchorage-independent growth; (4) stimulation of angiogenesis; (5) evasion of programmed cell death (apoptosis); and (6) ability to grow independently of stimulation by growth factors.  

THE MOLECULAR BASIS OF METASTASIS

All of the above mutations, whether acquired by chance accumulation or through clonal expansion of a cell population through selective pressure in a continued hostile environment, result in successful growth of a cancer cell population at the primary site. Only a small subset of the billions of cells within a tumor accumulates the traits of tissue invasion, extravasation, survival in the circulation, and growth in secondary sites that characterize successful metastases. This subset of cells has characteristics heralded by a change in the cancer cell phenotype observed as an epithelial-mesenchymal shift and is the result of reactivation and the loss of regulation of cellular programs associated with wound healing and/or embryogenesis.  

A cell that does not acquire the genetic alterations necessary for invasion and metastasis does not acquire a lethal phenotype and only rarely causes death. Several ongoing research efforts are aimed at differentiating/predicting which tumors have acquired the necessary signature that correlates with metastasis and/or poor prognosis. By comparing the genes that are expressed between primary cancers and metastases, Ramaswamy and colleagues identified a 17-gene expression signature that was able to distinguish primary tumors from metastases in several solid tumors and was associated with poor prognosis (Table 1).  

Other investigators have identified unique gene sets that function as metastasis signatures in multiple solid tumors, including breast, renal, colon, oral, lung, and prostate cancers. Similarly, several disease-specific gene signatures that distinguish aggressive cancers (in general, those cancers that recurred, metastasized, or caused death) from nonaggressive cancers (those that did not recur or metastasize) have been
For example, Glinksy and colleagues published an 11-gene signature panel with which they demonstrated a significant association between the expression pattern of the 11-gene signature and poor prognosis of patients with a wide variety of cancers (Table 1).\textsuperscript{21}

Hundreds of large-scale DNA microarray experiments have been performed that have generated quantitative profiles of gene expression in cancer, allowing types of cancer to be distinguished by their gene expression patterns and, more importantly, to discover novel molecular subtypes of cancer that are associated with a variety of tumor properties, including mechanism of transformation, propensity to metastasize, and sensitivity or resistance to particular therapies.\textsuperscript{35,36} Oncomine\textsuperscript{TM} is an online initiative that collects published cancer microarray data and allows researchers to easily compare genetic expression data across cancer types and subtypes (www.oncomine.com).\textsuperscript{37–39} We reviewed 14 cDNA microarray data sets of primary versus metastatic tumors within the Oncomine data set and found that no 2 cancers presented similar gene signatures and that the number of statistically significant ($P < 0.01$) genes that were differentially expressed varied from one study to another; thus, no consistent gene set has been identified that predicts the lethal phenotype of cancer (ie, metastatic disease) across multiple organ sites. It is likely that this is due to the fact that no investigators have compared gene signature sets to the clinical syndromes such as cachexia, thrombosis, and bone metastases that are ultimately responsible for the death of the patient.\textsuperscript{40} Although no direct research has been done to identify molecular signatures associated with these syndromes, when the different signatures are characterized by ontological process rather than specific function, we found that they fall into general categories that include RNA processing, cell proliferation, cell cycle and cell division, extracellular matrix alteration, and differentiation (Table 1). Increased RNA processing leads to the increased protein synthesis necessary for the more metabolically active cancer cells; increased cellular proliferation and cellular division lead to increased tumor burden; alterations in the extracellular matrix are important for the establishment of the proper “fertile bed” of the microenvironment that will support tumor growth; and loss of differentiation correlates with the activation of embryonic genes necessary for cell movement.\textsuperscript{2–5,13–15} These studies are further complicated by the fact that many of them analyze not only the cancer cells but also the supporting stromal tissues at the same time. Recent evidence suggests that the inherited genomic makeup of an individual may predict the frequency and future sites of metastasis by providing a favorable microenvironment for metastasizing cells to colonize.\textsuperscript{41–43} Many investigators are now concentrating on using laser-capture microdissection to characterize the individual cell populations of
TABLE 1 Gene Signatures from Three Independent Laboratories Defining Molecular Signatures of Metastasis, Poor Prognosis, and High-Versus Low-risk Patients

| Glinsky GV, Berezovska O, Giinskii AB<sup>21</sup> | Poor Prognosis |
| --- | --- |
| **Gene** | **Name** | **Function** |
| **UP** | | |
| GBX2 | Gastrulation brain homeobox 2 | Development |
| K67 | Antigen identified by monoclonal antibody KI-67 | Nuclear antigen present in proliferating cells |
| CCNB1 | Cyclin B1 | Regulatory protein involved in mitosis |
| BUB1 | BUB1 budding uninhibited by benzimidazoles 1 homolog | Kinase involved in spindle checkpoint function |
| KNTC2 | Kinetochore associated 2 | Spindle checkpoint signaling |
| USP22 | Ubiquitin-specific peptidase 22 | Cell-cycle control |
| HCF1C | Host cell factor C1 (VP16-accessory protein) | Regulation of cell cycle and transcriptional activity |
| RNF2 | Ring finger protein 2 | Polycomb group protein involved in transcriptional regulation |
| ANK3 | Ankyrin 3, node of Ranvier (ankyrin G) | Integral membrane protein involved in motility, proliferation, and activation |
| FGFR2 | Fibroblast growth factor receptor 2 | Growth |
| CES1 | Carboxylesterase 1 | Hydrolize long-chain fatty acid esters |

| Varambally S, Yu J, Laxman B, et al<sup>22</sup> | High Risk Versus Low Risk |
| --- | --- |
| **Gene** | **Name** | **Function** |
| **UP** | | |
| ITGA5 | Integrin, α 5 (fibronectin receptor, α polypeptide) | Form a fibronectin receptor |
| CIAP | Baculoviral IAP repeat-containing 2 | Inhibits apoptosis |
| DRB7P67 | Interleukin enhancer binding factor 3, 90kDa | Transcription factor |
| KRIP-1 | Tripartite motif-containing 28 | Transcriptional control |
| AMACR | α-Methylacyl-CoA racemase | Conversion of pristanoyl-CoA and C27-bile acyl-CoAs to their (S)-stereoisomers |
| OCLN | Occludin | Integral membrane protein that is located at tight junctions |
| MCM2 | MCM2 minichromosome maintenance deficient 2, mitotin | Initiation of eukaryotic genome replication |
| NUP62 | Nucleoporin p62 | Components of the nuclear pore complex in eukaryotic cells |
| LAP2 | Thymopoietin | Regulation of nuclear architecture by binding lamin B1 |
the tumor microenvironment, including the cancer cells, endothelial cells, and fibroblasts. 44–46

THE BYPRODUCTS OF METASTATIC TUMOR CELLS AND THEIR INTERACTION WITH THE MICROENVIRONMENT

The multiple factors produced during the process of metastasis that contribute to the morbidity and mortality of patients come from 3 sources: the cancer cells themselves, normal cells that are trying to inhibit the growth and spread of the cancer, and the factors that are released by the local microenvironment of the tissue as these cells interact (Table 2).

A critical event occurs in a metastasis when the growth of the tumor cell mass reaches approximately 1 cubic millimeter in size. 47 At this point, cells in the center of the tumor are beyond the diffusion distance of oxygen and other nutrients necessary for survival. Hypoxia, through the induction of hypoxia-inducible factor-1α, causes the production of multiple cytokines and growth factors that increase the chance of cell survival and turn on the cellular programs that promote growth, angiogenesis, and metastasis. 2–5,9,13–15

These include autocrine motility factor, urokinase plasminogen activator (uPA), matrix metalloproteinases (MMPs), cathepsins, endothelin-1

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### TABLE 2 Common Cytokines and Factors That Play a Role in the Production of the Lethal Phenotype

| Selected Cytokines and Factors | Role in Production of the “Lethal Phenotype” of Metastatic Disease |
|-------------------------------|---------------------------------------------------------------|
| **Chemokines**                |                                                               |
| CCL2/CCR2                     | Facilitates invasion and metastasis, promotes cancer cell growth by autocrine regulation, contributes to regulation of angiogenesis |
| CXCL12/CXCR4                  | Regulates stem cell homing and plays a crucial role in facilitating those tumors that metastasize to bone |
| **Cytokines**                 |                                                               |
| IL-1                          | Contributes to ability to metastasize; implicated as a tumor cell growth factor; stimulates angiogenic factors; implicated in thrombosis, cachexia, and bone metastases |
| IL-6                          | Promotes cancer growth; implicated as a tumor cell growth factor; stimulates angiogenic factors; implicated in thrombosis, cachexia, and bone metastases |
| NF-κB                         | Key mediator and regulator of the inflammatory process, participates in feedback loop of proinflammatory cytokines, suppresses apoptosis, promotes tumor invasion and metastasis, contributes to tumor proliferation by activating the expression of growth factor genes, contributes to genomic instability of the cancer cells |
| TNF-α                         | Induces DNA damage and inhibits DNA repair, promotes tumor growth, induces angiogenic factors, key in initiation of inflammatory cascade, regulates chemokines, contributes to ability for invasion, contributes to cachexia syndrome, implicated in thrombosis, contributes to bone metastases |
| TGF-β                         | Contributes to angiogenesis, implicated in thrombosis, contributes to bone metastases |
| VEGF                          | Induces tumor angiogenesis in solid tumors and promotes tumor growth and metastasis |
| **Proteases**                 |                                                               |
| MMP                           | Enzyme involved in degradation of extracellular matrix and is upregulated in most cancers, allowing tumor cell invasion and metastasis |
| uPA                           | uPA levels in both resected tumor tissue and plasma are of independent prognostic significance for patient survival in several types of human cancer |
| **Coagulation cascade**       |                                                               |
| Thrombin                      | Thrombin generation is crucial for metastasis through fibrin and platelet deposition; thrombin receptor upregulation has been reported in a variety of malignant tissues |
| TF                            | Advanced cancer is associated with a hypercoagulable state that is triggered by TF; TF significantly participates in tumor-associated angiogenesis, and its expression levels have been correlated with the metastatic potential |
| **Cell–cell interactions**    | Cell–cell, cell–platelet, and platelet–platelet interactions appear to enhance metastasis |

CCL2/CCR2 = monocyte chemotactic protein-1 and its receptor.
CXCL12/CXCR4 = stromal-derived factor-1 and its receptor.
IL-1 = interleukin-1.
IL-6 = interleukin-6.
NF-κB = nuclear factor κB.
TNF-α = tumor necrosis factor-α.
TGF-β = transforming growth factor-β.
VEGF = vascular endothelial growth factor.
MMP = matrix metalloproteinase.
uPA = uroplasminogen activator.
TF = tissue factor.
The interaction of cancer cells with the normal cells of the patient also results in the production of multiple factors that may be detrimental to the host. A relationship between cancer and the inflammation associated with host response has been recognized since the 1860s, when Virchow observed leukocytes in neoplastic tissues. While some cancers are associated with an inflammatory response that is detrimental to the tumor, there are several malignancies that appear to be facilitated by chronic states of inflammation, including *Helicobacter pylori* and gastric cancer, acid reflux and esophageal cancer, and inflammatory bowel disease and colon cancer. These cancers are thought to be the result, in part, of the production of proinflammatory cytokines by the host immune cells as they try to destroy the cancer cells. Proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-11 (IL-11), and TGF-β, have been shown to induce DNA damage and inhibit repair; inhibit apoptosis; facilitate tumor growth, invasion, and metastasis; induce production of angiogenic factors; and contribute to maintaining a chronic state of inflammation by way of a self-activating feedback loop. These cytokines can cause morbidity and mortality in patients through activation of multiple signaling pathways leading to clinical syndromes such as cachexia and coagulopathy.

Similarly, the interaction of other host cells with cancer cells can lead to alterations in the microenvironment. Perhaps the best characterized example of this is metastases involving the bone. Prostate and breast cancer cells, for example, are attracted to the bone by high levels of stromal-derived factor-1 (SDF-1), a chemokine secreted by bone stromal cells that helps direct hematopoetic cell trafficking in and out of the bone marrow. Once there, they secrete several cytokines, including IL-6, IL-1, TNF-α, TGF-β, epidermal growth factor (EGF), and ET-1, that stimulate the maturation and proliferation of osteoblasts. Osteoblasts in turn build up disorganized bone, as well as secrete receptor activator of nuclear factor κB ligand (RANKL), which binds to receptor activator of nuclear factor κB (RANK) on osteoclast precursors, resulting in maturation and subsequent osteolysis of the bone matrix. This breakdown of the bone matrix in turn releases growth factors that stimulate the tumor cells to grow further, resulting in a vicious cycle of bone destruction and further tumor growth.
that need to be explored at both the molecular and clinical levels. These analyses suggest that multiple cytokines/combinations of cytokines cause morbidity and mortality for cancer patients and offer multiple avenues for therapeutic development that need to be addressed.

THE CLINICAL SYNDROMES RESULTING FROM THE GROWTH OF METASTATIC TUMOR CELLS

Clinically, the “lethal” phenotype of cancer is defined by what kills the patient. Data from autopsy series document where metastasis occurs, but rarely clearly document how cancer ends a patient’s life. We performed an extensive literature search through PubMed and Google Scholar to identify published autopsy series that documented sites of metastases in cancer patients at the time of death (Table 3). The majority of the published autopsy data on cancer patients was gathered between 1900 and the 1970s and is representative of deaths when little treatment was available beyond surgery and radiation. For
example, very few modern series are available that report metastases in patients receiving treatments such as chemotherapy that may alter the natural history of the disease. Similarly, while these series report anatomic distribution, actual cause of death is rarely delineated. The major sites of metastases in patients dying of cancer are the lymph nodes, the lungs, the liver, and the skeleton (Table 3). Although how patients die from cancer depends on metastatic patterns of specific tumor types, the clinical syndromes by which patients succumb to cancer can be roughly divided into 2 categories: death due to specific organ involvement with subsequent functional failure such as seen in many patients with metastases to the brain, or death due to poorly defined factors that lead to a complex cascade of biological responses eventually culminating in progressive weight loss, anorexia, anemia, metabolic alterations, asthenia, depletion of lipid stores, and severe loss of skeletal muscle protein (Figure 3).

Cachexia

The incidence of cachexia varies by tumor type, with the highest frequency (83% to 87%) in patients with pancreatic and gastric cancer; intermediate frequency (48% to 61%) in patients with colon, prostate, lung, and unfavorable non-Hodgkin lymphoma; and lowest frequency (31% to 40%) in patients with breast cancer, sarcomas, leukemia, and favorable subtypes of non-Hodgkin lymphoma. Approximately 20% of cancer deaths overall are attributable to cachexia, with death typically occurring when weight loss approaches 30%.

The inflammatory cascade set in place by host and tumor results in an imbalance between proinflammatory cytokines (including lipolytic factor zinc α-2 protein (ZAG), proteolysis-inducing factor (PIF), TNF-α, IL-1, IL-6, and interferon-γ) and anti-inflammatory cytokines (including interleukin-4, interleukin-12, and interleukin-15) (Figure 4). These cytokines act on multiple targets, including myocytes, adipocytes, hepatocytes, bone marrow, endothelial cells, and neurons, leading to a complex cascade of biological responses eventually culminating in progressive weight loss, anorexia, and reduced fat oxidation, and reduced lipogenesis as a result of activation of futile and energy-inefficient cycles. Tumors consume a large amount of glucose and convert it to lactate, leading to an anaerobic environment that does not provide a high enough oxygen tension for the Krebs cycle and mitochondrial oxidative phosphorylation to operate. As a result, the Cori cycle, a much less energy-efficient cycle, is used for gluconeogenesis.

In addition, patients often develop glucose intolerance, insulin resistance, increased glucose consumption, increased fat oxidation, and reduced lipogenesis as a result of activation of futile and energy-inefficient cycles. Tumors consume a large amount of glucose and convert it to lactate, leading to an anaerobic environment that does not provide a high enough oxygen tension for the Krebs cycle and mitochondrial oxidative phosphorylation to operate. As a result, the Cori cycle, a much less energy-efficient cycle, is used for gluconeogenesis.

There is an overall increase in lipolysis in patients with cancer, resulting in the utilization of lactate and fatty acids, which can be utilized for gluconeogenesis with inhibition of lipogenesis contributing to depletion of fat stores. The muscle hypercatabolism observed in cancer cachexia is thought to be dependent on hyperactivation of the calcium-dependent (calpains) and the ATP-ubiquitin-

### Table 3: Frequent Sites of Metastases of Common Cancers

| Primary Site | Total Cancer Deaths (%) | Frequency of Metastasis (%) (at Autopsy) | Lymph Node | Lung | Pleura | Liver | Bone | Brain |
|--------------|-------------------------|----------------------------------------|------------|------|-------|------|------|-------|
| Lung         | 31†/26‡                  | 92–93§                                 | 40         | 28   | 51–55 | 30–41| 21–50¶ |
| Breast       | 15§                     | 80–97                                  | 60–62      | 36–47| 49–61 | 47–80| 5–36  |
| Colon        | 10                      | 25–77                                  | 12–54      | 14   | 36–81 | 1–18 | 1–8   |
| Prostate     | 9†                      | 71–87                                  | 15–64      | 13–18| 28–71 | 79–91| 2–13  |
| Pancreas     | 6                       | 50–88                                  | 25–49      | 18   | 75–78 | 16–18| 2     |
| Ovary        | 6†                      | 58–91                                  | 10–37      | 33   | 42–51 | 12–15| 1–4   |
| All epithelial cancers | 93†/91‡ | 87                                    | 48         | 22   | 41    | 32   | 8     |

* Percent of estimated total cancer deaths in 2005 as reported by the American Cancer Society.† Male-specific percentage.‡ Female-specific percentage.§ Frequency range as reported from multiple autopsy series.57–70 Single-digit frequency as reported.59 ¶ Histologic-subtype dependent.
dependent proteolytic pathways by cytokines. The progressive loss of muscle mass observed in patients with cancer cachexia contributes significantly to overall functional impairments, respiratory muscle weakness, and decreased immunity, ultimately culminating in death of the patient. Treatment of cancer cachexia was initially aimed at nutritional intervention. However, aggressive nutritional therapy did not show significant improvement in weight, lean body mass, performance status, or quality of life. The understanding of the signal transduction and metabolic pathways associated with cancer cachexia has opened several areas of potential as well as active investigation to help patients suffering from this syndrome (Table 4). Current therapies focus on affecting the hunger pathways with goals of increasing appetite and inhibiting catabolic factors. One approach to increasing appetite is to modify hypothalamic-derived signals to suppress cachexia. The best-known agents of this type are megestrol and medroxyprogesterone acetate. Several randomized trials have shown these agents to increase appetite and caloric intake and stabilize weight; however, the weight gain has been attributed to water and fat and not lean muscle tissue. It is unclear how well these agents affect morbidity and mortality. Other agents that affect central nervous system signaling are under active development, including melatonin receptor antagonists and agouti-related protein, as well as neuropeptide Y mimetics.

In addition to central nervous system manipulations to treat cachexia, affecting hormones that act in periphery in muscle and fat cells also holds promise for cachexia treatment. Growth hormone, as well as growth hormone-releasing hormone, which stimulate increase in muscle mass, have not been studied to ameliorate cancer cachexia. Insulin resistance, although counterintuitive in a patient population with little adiposity, occurs due to activation of adipocytes with release of free fatty acids. Therefore, treatment of cancer cachexia with a class of drugs known to enhance tissue insulin sensitivity, such as the thiazolidinediones, may be of therapeutic benefit. These drugs function as high-affinity ligands for peroxisome proliferator-activated receptor-γ, which is the nuclear receptor in fat

FIGURE 4 The Cachexia Syndrome. The inflammatory cascade set in place by host and tumor result in an imbalance between proinflammatory cytokines that act on multiple targets, including myocytes, adipocytes, hepatocytes, bone marrow, endothelial cells, and neurons, leading to production of a complex cascade of biological responses eventually culminating in progressive weight loss, anorexia, anemia, and asthenia. TC = tumor cell; IL-1 = interleukin-1; IL-6 = interleukin-6; IL-11 = interleukin-11; LMF = lipid-mobilizing factor; IFNγ = interferon gamma; TNF-α = tumor necrosis factor-α; PIF = proteolysis-inducing factor.
cells that is thought to be associated with weight gain in type II diabetes.\textsuperscript{86} This class of drugs may also suppress the hyperinsulinemia seen with cachexia that activates the hypothalamic axis, resulting in decreased orexigenic signaling.

NF-\(\kappa\)B has also been implicated in playing a major role in cancer cachexia. By interaction with proinflammatory cytokines, NF-\(\kappa\)B activation leads to suppression of myogenesis. Therefore, inhibition of NF-\(\kappa\)B is postulated to stimulate recovery of lost muscle mass.\textsuperscript{86} Several agents interfere with the synthesis and release of these cytokines by interfering with NF-\(\kappa\)B, including eicosapentaenoic acid, dehydroepiandrosterone, pentoxifylline, curcumin, resveratrol, dehydroxymethylepoxyquinomicin, and sodium salicylate.\textsuperscript{86–88} Fearon et al recently reported a trial comparing eicosapentaenoic acid to placebo for treatment of cancer cachexia in a double-blind, placebo-controlled trial of 518 patients with advanced gastrointestinal and lung cancer that demonstrated no increase in survival. This trial may have been negative because these types of agents may need to be utilized earlier at the onset of cachexia.

The major proinflammatory cytokines associated with cancer cachexia, TNF-\(\alpha\), IL-1, and IL-6, all offer potential targets for therapy. Monoclonal antibodies that inhibit TNF-\(\alpha\) have been utilized in small trials to treat cancer-associated cachexia, but have not demonstrated much activity.\textsuperscript{89,90} This may be because TNF-\(\alpha\) levels vary in patients, and antibody therapy may need to be targeted to patients with high levels of particular cytokines. Other potential therapies include the recombinant interleukin-1 receptor (rIL-1r) antagonist anakinra and antibodies to IL-6, both of which are in clinical trials for rheumatoid diseases.\textsuperscript{96–98} It has become clear that cachexia is a multifactorial process that will likely need to be approached from different angles. Much like the disappointing results of single-agent therapy for treating cancer itself, we should not be disappointed from trials of single interventions, as ultimately a combination approach will be needed.

**Thrombotic Syndromes**

The association between venous thromboembolism, coagulopathy, and malignancy was first made by Trousseau in 1877, with his description of migratory thrombophlebitis and pancreatic cancer.\textsuperscript{91} Since that time, thrombosis has become recognized as a common complication of cancer associated with significant morbidity and reduced survival.\textsuperscript{92,93,99} Although coagulopathy is only directly related to death in approximately 10% of cases, it has been demonstrated to be present in as high as 50% of patients at the time of death.\textsuperscript{100–104}

The characteristics that facilitate cancer cells’ ability to invade locally and metastasize also result in damage to endothelial cells and activation of the coagulation cascade, resulting in Virchow’s triad of hypercoagulation, stasis, and endothelial cell damage (Figure 5). The procoagulant,
fibrinolytic, and proaggregating activities of tumor cells set up the perfect local environment for thrombosis. To break down the surrounding microenvironment and allow the tumor mass to grow, the cancer cells to move, and growing blood vessels to reach the tumor mass, the cellular programs that are used in wound healing are activated, and cytokines and growth factors are released that have local and systemic effects. These factors include thrombin, VEGF, TNF-α, interleukin-1 β, uPA, MMPs, cathepsins, and tissue factor (TF).

TF, for example, is physiologically involved in initiating molecular events leading to hemostasis by formation of a Factor VII/TF complex. The hemostatic process leads to activation of thrombin and, therefore, conversion of fibrinogen to fibrin and formation of clot at the site of vascular injury. In addition, the formation of new blood vessels associated with tumor growth results in changes in vascular permeability, extravasation of plasma proteins, microhemorrhage, extravascular clotting, and fibrinolysis, which contributes to the formation of a scaffolding for new vessel development, but at the same time results in disruption of the normal homestatic balance between coagulation and anticoagulation. Constitutive or excessive production of TF by tumor cells, however, leads to pathologic thrombosis and angiogenesis.

The potential to inhibit coagulopathies and thrombosis in cancer patients is enhanced by the development of multiple agents for the treatment of cardiovascular conditions. Multiple studies have suggested that treatment with anticoagulation via warfarin or various heparins in addition to chemotherapy leads to increased survival in patients with a variety of cancers; however, the magnitude of the effect of anticoagulation on morbidity and mortality for cancer patients remains unclear.

Multiple new agents that inhibit the clotting pathway are available for clinical trials in cancer patients and include the direct thrombin inhibitors, recombinant thrombomodulin, and inhibitors of TF.

Factors secreted by the cancer cells, including MMPs, uPA, and cathepsins, break down...
the extracellular matrix of the tumor microenvironment and interrupt vascular integrity. Several small molecule inhibitors and antibodies to these molecules have been investigated as single agents and in combination with chemotherapies for the treatment of multiple types of cancer.\textsuperscript{117–123} These trials have focused on tumor progression and/or survival, and their activity regarding decreasing morbidity and mortality as related to decreasing thrombosis has not been investigated.

The rheumatoid diseases have provided the cancer community with a paradigm for the treatment of diseases based on the inhibition of proinflammatory cytokines. The prototypical agents are the monoclonal antibodies that inhibit TNF-\( \alpha \).\textsuperscript{89,90} As noted above, anti-TNF-\( \alpha \) strategies may have value in a subset of patients suffering from cachexia. TNF-\( \alpha \), however, also plays a role in inflammation associated with vascular injury. Similarly, IL-1 is a proinflammatory molecule that also has a role in thrombosis, and an inhibitor used in rheumatoid diseases, anakinra, is available for clinical trials.\textsuperscript{91} Small-molecule inhibitors and antibodies directed against other cytokines such as IL-6 and TGF-\( \beta \) are also in clinical development.\textsuperscript{92,93,124–126} Trials need to be designed with an eye to their effect on morbidity and mortality associated with coagulaopathy (Table 5).

**Bone Involvement**

Bone involvement is the main cause of direct cancer pain. Skeletal involvement is present in an average of 32\% of cancer patients at autopsy, with much higher prevalence in patients with lung, breast, kidney, and prostate cancers. In recent careful autopsy studies, 100\% of men who die of prostate cancer have bone involvement.\textsuperscript{51,62} As previously described, the activation of osteoblasts and osteoclasts by cancer cells results in a vicious cycle of bone destruction and increased tumor growth, resulting in pain, fractures, and spinal cord compression (Figure 6). In a significant proportion of patients, this pain requires narcotic analgesia. Patients require higher and higher doses of opioid analgesics, resulting in somnolence, sometimes with subsequent aspirations and/or coma. Review of the autopsy series literature did not reveal what percentage of cancer patients die with concurrent aspiration.\textsuperscript{56–70} In our current autopsy series of 48 patients who died of metastatic prostate cancer, concurrent aspiration pneumonia was documented in fewer than 10\% of cases.\textsuperscript{62}

| Contributor to Thrombosis | Examples of Potential Treatments |
|---------------------------|---------------------------------|
| Thrombin                  | Warfarin, hirudin, argatroban, rThrombomodulin\textsuperscript{107–109,112,115} |
| TF                        | Heparins, pentasaccharide, mAb (6A6)\textsuperscript{109,114–116} |
| MMPs                      | Small molecules (BMS-27529, tanomastat)\textsuperscript{117–119} |
| uPA                       | Small peptide (A6)\textsuperscript{120,121} |
| Cathepsins                | Small molecules (relacatib), AAE581\textsuperscript{122,123} |
| Cytokines                 | mAbs (lerdelimumab, metelimumab), antisense (AP12009)\textsuperscript{124–126} |
| TGF-\( \beta \)           | mAbs (etanercept, infliximab, adalimumab)\textsuperscript{93,95} |
| TNF-\( \alpha \)          | rIL-1r antagonist (anakinra)\textsuperscript{91} |
| IL-1                      | mAbs (tocilizumab, CNTO328)\textsuperscript{92,93} |
| IL-6                      | Warfarin, heparins\textsuperscript{109,111} |

\( \text{TF} \) = tissue factor.
\( \text{MMPs} \) = matrix metalloproteinases.
\( \text{uPA} \) = uroplasminogen activator.
\( \text{TGF-}\beta \) = transforming growth factor-\( \beta \).
\( \text{TNF-}\alpha \) = tumor necrosis factor-\( \alpha \).
\( \text{IL-1} \) = interleukin-1.
\( \text{IL-6} \) = interleukin-6.
\( \text{mAb} \) = monoclonal antibody.
\( \text{rIL-1r} \) = recombinant interleukin-1 receptor.

The rheumatoid diseases have provided the cancer community with a paradigm for the treatment of diseases based on the inhibition of proinflammatory cytokines. The prototypical agents are the monoclonal antibodies that inhibit TNF-\( \alpha \).\textsuperscript{89,90} As noted above, anti-TNF-\( \alpha \) strategies may have value in a subset of patients suffering from cachexia. TNF-\( \alpha \), however, also plays a role in inflammation associated with vascular injury. Similarly, IL-1 is a proinflammatory molecule that also has a role in thrombosis, and an inhibitor used in rheumatoid diseases, anakinra, is available for

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**TABLE 5 Potential Treatments to Prevent Thrombotic Syndromes in Cancer Patients**
Approximately one third of the patients were in an opioid-induced coma at the time of death and had no other discernible cause of death at autopsy.

The bone microenvironment presents several potential targets that mediate the effects of the vicious cycle of bone destruction. The endothelial cells, osteoblasts, and osteoclasts that interact with the tumor cells all present targets for modulation (Figure 6, Table 6). Clinical trials of the ET-1 receptor antagonist atrasentan to inhibit osteoblasts have been completed and are ongoing. Osteoclast destruction can be inhibited by Food and Drug Administration–approved bisphosphonates such as zoledronate and by radioactive isotopes that bind to hydroxyapatite (samarium, strontium). Osteoclast function can also be inhibited by the src tyrosine kinase inhibitors, as well as by targeting the osteoblast–osteoclast axis through the inhibition of RANKL. Multiple studies are utilizing inhibitors of VEGF to target tumor-related endothelial cell proliferation in bone metastases, both as single agents, as well as in combination with chemotherapy.

Soluble factors and cytokines secreted by the tumor cells, as well as cells in the bone microenvironment, also provide an array of targets. As noted previously, delineating potential targets for inhibiting thrombosis, MMPs, and cathepsins break down the extracellular matrix and promote tumor cell growth, invasion, and metastasis. Small-molecule and antibody inhibitors of these enzymes have demonstrated activity in a variety of cancers, including metastatic prostate cancer. EGF antibodies have demonstrated antitumor activity, but also may inhibit stimulation of endothelial cells and osteoblasts. Stromal–derived factor-1 is a cytokine that has been implicated in the homing of cancer cells to the bone. AMD3100 is a small-molecule inhibitor of stromal–derived factor-1 (SDF-1, CXCL12), first developed for HIV infection, that could potentially inhibit propagation of metastases to the bone microenvironment. Monocyte chemoattractant protein–1 (MCP-1, CCL2) is a cytokine that attracts cancer cells, as well as proinflammatory macrophages.
to the bone microenvironment. The inhibition of this cytokine by the antibody CNTO888 appears to have direct cytotoxic effects through inhibition of tumor cell proliferation, as well as inhibition of the infiltration of macrophages into the tumor microenvironment that promotes tumor growth and angiogenesis.141 As previously detailed, antagonists to the cytokines TGF-β, TNF-α, IL-1, and IL-6 may all be important in ameliorating the effects of the vicious cycle of tumor-microenvironment interactions that leads to pain caused by bone destruction.89–93,96–98,124–126

Dyspnea occurs in 20% to 80% of patients with cancer and is severe in 10% to 60% of patients, especially in the last 6 weeks of life.142–145 Breathing is controlled by the respiratory center (integrates all peripheral and central afferent input and generates efferent activity resulting in respiration), chemoreceptors (sense small changes in pH and pCO2), and mechanoreceptors (respond to irritants and stretching of airways). The cause of dyspnea in a given patient is usually multifactorial, stemming from direct lung involvement, local and systemic cytokine production, treatment-related causes, and underlying diseases such as congestive heart failure and chronic obstructive pulmonary disease (Table 7).

Table burden occupying the lung parenchyma, pulmonary lymphangitic spread of

### TABLE 6 Potential Therapeutic Targets in the Bone Microenvironment

| Target                  | Examples of Potential Treatments |
|-------------------------|-----------------------------------|
| Osteoblast              | Endothelin receptor (atrasentan)  |
| Osteoclast              | Hydroxyapatite (zoledronate, samarium, strontium) |
|                         | src tyrosine kinase (dasatinib)    |
|                         | RANKL (mAb denosumab)              |
| Endothelial cells       | VEGF (mAb bevzumab, VEGF Trap)     |
|                         | VEGF r tyrosine kinase (BAY43–9008, PTK787, ZD6474) |
| MMPs                    | Small molecules (BMS-27529, tanomastat) |
| Cytokines               | Small molecules (relacatib, AA581) |
| TGF-β                   | mAbs (lerdelimumab, metelimumab), antisense (AP12009) |
| TNF-α                   | mAbs (etanercept, infliximab, adalimumab) |
| IL-1                    | rIL-1r antagonist (anakinra)       |
| IL-6                    | mAbs (tocilizumab, CNTO328)       |
| CXCL12/CXCR4 (SDF1)     | Small molecule (AMD3100)           |
| CCL2/CCR2 (MCP1)        | mAb (CNTO888)                      |
| Epidermal growth factor | EGFr mAbs (gefitiib, cetuximab, erlotinib, laputinib, trastuzumab) |

MMPs = matrix metalloproteinases.
TGF-β = transforming growth factor-β.
TNF-α = tumor necrosis factor-α.
IL-1 = interleukin-1.
IL-6 = interleukin-6.
SDF1 = stromal-derived factor-1.
MCP1 = monocyte cheomatractant protein-1.
RANKL = receptor activator of nuclear factor κB ligand.
mAb = monoclonal antibody.
VEGF = vascular endothelial growth factor.
VEGFr = vascular endothelial growth factor receptor.
rIL-1r = recombinant interleukin-1 receptor.
EGFr = epidermal growth factor receptor.

### TABLE 7 Causes of Dyspnea in Malignancy

| Dyspnea directly related to cancer |
|------------------------------------|
| Parenchymal tumor mass             |
| Lymphangitic spread                |
| Pleural effusion                   |
| Superior vena cava syndrome        |
| Pericardial effusion               |
| Ascites                            |
| Dyspnea indirectly related to cancer |
| Cachexia                           |
| Anemia                             |
| Infection                          |
| Emboli                             |
| Deconditioning                     |
| Dyspnea related to cancer treatment |
| Radiation/chemotherapy-induced pneumonitis |
| Radiation/chemotherapy-induced percarditis |
| Surgical resection of lung parenchyma |
| Dyspnea unrelated to cancer or cancer treatment |
| Pulmonary disease (chronic obstructive pulmonary disease, asthma) |
| Cardiac disease (coronary artery disease, congestive heart failure) |
| Anxiety                            |
| Obesity                            |
disease, malignant pleural effusions, and pulmonary embolism are common, well-recognized causes of dyspnea. Treatment of cancer itself can contribute to the dyspnea experienced by patients through radiation-or chemotherapy-induced pneumonitis and drug-related pleural effusions, through pneumonia secondary to neutropenia, and through tachypnea due to anemia. Cachexia can result in respiratory muscle weakness. Inactivity can lead to deconditioning, and decreased consciousness from pain control can also lead to deconditioning, as well as aspiration pneumonia.

Cancer-related dyspnea is generally considered to be a late event in the disease course, and systematic approaches to treatment beyond targeting identifiable causes such as anemia have not been undertaken. It is speculative, but likely, that inhibition of the proinflammatory cytokines that have already been delineated above may have a role in decreasing the morbidity and mortality associated with dyspnea.

CONCLUSION AND IMPLICATIONS

The disease cancer is the result of a complex interplay between the growing tumor and local and systemic responses by the patient to the presence of malignancy. Traditionally, cancer therapy has focused on cytotoxic agents rather than therapies that ameliorate the effects of byproducts of the cancer cells or the proinflammatory host response to their presence. Insight into the molecular events underlying the lethal clinical syndromes that contribute to the morbidity and mortality of cancer patients suggests avenues of treatment, many of which have already been explored in other disease settings.

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