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Unveiling the Pathogenesis of Geriatric Oncology: Mystery Unfolded

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Abstract

The vast entity of the aging process must be well thought out while considering optimal management for elderly patients with cancer. Co-morbidity and functional status are the key factors which determine the overall survival of patients. Multidisciplinary approaches to patient management must be emphasized and stressed to deal with end-of-life issues. Researchers need to identify elderly people who are most susceptible to treatment toxicities and must deal with palliation and hospice care for these patients. One approach to the issue of aging as a variable in treatment outcome would be to utilize programs and facilities supported by cancer institutes to address age-related questions in clinical trials. Academic oncologists, geriatricians and pathologists can create realistic and imminent goals to achieve victory against cancer and provide optimal treatment that includes adequate supportive care and reduces the burden of post-treatment morbidities that compromise quality of life in these patients. This review focuses on the basis of cancers that affect the elderly and how momentous advances can be obtained to expound the pathways most critically involved in tumor development and progression. Through this review, an attempt has been made to explain the impact of peculiar mutations and altered cell behavior underlying geriatric oncogenesis.

Keywords: Cancer, Co-morbidity, Mutations, Geriatric, Multidisciplinary, Palliation, Supportive care

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Introduction

The progressive aging of the population has been accompanied by an increase in cancer incidence.[1] More than 60% of all tumors occur after the age of 65 years, with more than two-thirds of tumor deaths in people older than 70 years.[2] Significant progress has been made in understanding the genetic basis of

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molecular and cellular aspects of ageing and gerontology. Accumulations of innumerable factors which embrace aberrant genetic alterations, cell senescence, multi-step carcinogenesis, apoptosis, and angiogenesis form the basis for the progression from a normal cell to a dysplastic/malignant cell.[1, 3, 4] Despite the increasing incidence of cancer with population aging, only a minority of elderly patients have enrolled in clinical trials. Traditionally, patient selection has been based on good clinical practice that consists of clinical judgment with performance status and organ function parameters. However, there seems to be a need for a more comprehensive tool in pre-treatment assessment so that the potential problems in treating elderly patients can be predicted and avoided. Functional status is a significant consideration in the elderly. Since aging is the result of highly individualized processes, an assessment should be made for each patient in order to adequately plan the treatment. The most significant element is the goal of therapy in context of the overall condition of the patient. This goal, whether it is prolongation of survival, remission, cure, or palliation of symptoms must be clearly defined. This provides the patient and family with a view of the expectations of treatment and allows short and long-term planning. This review focuses on this aspect of cancer-related treatment in elderly patients who are largely left to fate with life crippling morbidities which should not go unnoticed.

Onco-science of gerontology

The process of aging is highly individualized and associated with systemic and physiological changes. Increased concentration of inflammatory mediators, such as interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and C-reactive protein (CRP) result from succession of inflammatory processes that fail to resolve completely.[5] Endocrine senescence is responsible for reduced protein synthesis, whereas immune senescence accommodates the development of infection leading to further accretion of cytokines in circulation.[4, 6, 7] The declining ability of senescent cells to repair DNA damage prolongs toxicity. The process of telomere shortening with cell division is relevant to cellular senescence and is important for organism aging and life span.[8, 9] Other factors that influence gene or protein functions include accumulation of damage over time due to extrinsic factors such as reactive oxygen species and ionizing radiation.[5, 9, 10] The hypothesis that free-radical damage is central to the process of carcinogenesis is an established concept.[11] It is apparent that molecular and sub-cellular factors are critical to cellular senescence and relevant to neoplastic transformation and tumor growth.[12]

Cellular senescence

The senescent state is associated with cell-cycle arrest which occurs after cells undergo an intrinsically defined number of divisions in-vitro. Derangements in pathways that lead to replicative senescence lead to uncontrolled growth.[13] Replicative senescence is induced as a result of an intrinsic mitotic counter, namely telomere shortening. Premature senescence describes senescence induced by extrinsic factors that act in a cell's replicative history. The senescent phenotype is indistinguishable, irrespective of the inducer. Factors known to induce premature senescence are oncogenic RAS, DNA damage and oxidative stress and it is well-known that these multiple factors are responsible for the ageing process.[14-16] Senescent cells in culture assume a larger size, remain metabolically active, and are more resistant to apoptotic death than pre-senescent cells. Senescent cells cannot be stimulated to exit the G1 phase of the cell cycle, synthesize DNA and proliferate; this reflects an innate resistance of such cells to respond to growth factor signals rather than a failure of growth factor signal transduction.[17-19] p53 and RB have been identified as tumor suppressor genes which exert their tumorigenic effect by enhancing replicative life span.[20] The accumulation of senescent cells creates an environment that is more sustainable for tumor growth as ageing proceeds.[21] Non-transformed cell types are important for the

successful development of a tumor. This might not reflect the accumulation of cells at the end of their replicative lifespan as a result of telomere shortening, but due to the accumulation of senescent genes triggered by other damaging pathways.[13, 22, 23]

Role of telomeres in senescence

Telomeres are complex sub-cellular structures that protect the ends of linear chromosomes. A telomere is considered to be 'capped' when it is sufficiently stable to signal continued proliferation to the cell and 'uncapped' when it triggers a cell-cycle arrest or apoptosis. The role of telomere shortening in tumorigenesis depends on the genetic context which might either promote or inhibit tumor formation. Telomere shortening triggers replicative senescence and causes genetic instability. Telomerase may also be a useful tumor-specific antigen and effective anti-tumor T-lymphocyte responses against TERT-expressing cells have been generated showing the potential for immunotherapy.[13, 24, 25]

Carcinogenesis and DNA repair

The universal feature of cancer is its ability for uncontrolled cell proliferation that cannot be checked by the normal cell kinetics regulators.[25] It is not uncertain that aging influences some parameters that render an individual susceptible or resistant to cancer.[3, 16] It appears that species and strain variations, presence or absence of organ dysfunction and carcinogenic dose are imperative predictors of carcinogenesis rather than host age. The most commonly mutated pathways in cancer are p53, the Erb B family of receptors and RAS. It is hence essential to focus on how mutation changes the network and can be used to identify new targets or treatment strategies.[26] The ubiquitous presence of a vast number of carcinogenic factors in our milieu and the formation of initiated cells are a frequent occurrence in the organs of aged individuals.[27]

Tumor angiogenesis

Onco-angiogenesis differs from physiological angiogenesis that includes aberrant vascular structure, altered endothelial-cell–pericyte interactions, abnormal blood flow, increased permeability and delayed maturation. The abnormal features of tumor vasculature result from a disproportionate expression of angiogenic cytokines and inhibitors. Tumor hypoxia complicates the angiogenic response depending on the status of p53 which regulates key angiogenic cytokines and inhibitors.[28] Angiogenic stimuli in the form of soluble factors such as fibroblast growth factor or lymphocyte-induced angiogenesis factor stimulate endothelial cell proliferation and new vessel formation.[25, 29] This is considered an important factor in age-associated reduced rates of tumor growth and spread.[13]

Aging, time and disease

The concept of time versus aging forms the heart of gerontology. Time is the standard which predicts ''aging,'' and it is appreciated that cells, tissues, organs, and individuals ''age'' at different rates. ''Aging'' is the phenotypic change that occurs over time and results in alteration of function or appearance.[12] Age is not infinite and cancer is not inevitable for all older persons.[30] Age is the greatest risk factor for the occurrence of malignancy and it is observed that for many tumors, growth and metastases occur at a slower rate in the elderly.[11] The disparity between decreased cancer aggressiveness in an individual and high rate of mortality is because the survival data are confused by problems that include co-morbidities, polypharmacy, physician bias regarding diagnosis and treatment in the elderly, and age-associated life stresses along with an inability to present to a medical center for treatment.[31]

Cancer chemotherapy in the elderly

The diversity of the geriatric population makes it difficult to define general rules for treatment with chemotherapy. Chemotherapy related myelosuppression, cardiotoxicity, peripheral and central neurotoxicity are common and more severe in elderly individuals. This toxicity is the result of

increased vulnerability of target organs and delayed excretion of renally excretable agents.[10] The development of new chemotherapy regimens with less toxicity and sufficient efficacy in elderly patients should be set as a priority for future research.[9]

Consideration of care

Treatment involves a combination of biological and tumor-related factors.[32] Cognitive impairment and delirium is a widespread problem in the elderly.[33] Dementia, depression, and hearing impairment delays assessment and treatment which requires patient cooperation and could make it difficult for patients to understand their treatment.[34] Outpatient care may be more cost-effective and convenient than inpatient care, but it has indirect costs that must be borne by the patients, their families or caregivers.[35] The effective management of cancer requires skills for general assessment of geriatric patients. A conjoint effort of oncologists, pathologists, surgeons and physicians needs to be sentient of novel data and ideas regarding the biology of aging and aspects of various treatment strategies. Prospective clinical trials in the elderly are critical to assess these strategies and develop data that clinicians can apply to optimize treatment needs in this set of severely compromised patients.[36]

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Authors' Contribution

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Conflicts of interest

The authors certify that they have no conflicts of interest.

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