



Cancer in The Elderly – Get Ready for The ‘Epidemic’

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“Every day you get older...that’s a law”

Butch Cassidy and the Sundance Kid

CANCER IN THE ELDERLY – MAGNITUDE OF THE PROBLEM

Our median life expectancy is increasing. A person surviving to the age of 75 years is now expected to live another 11 years and a person surviving upto 85 years is expected to live another six years.

Though cancer occurs at all ages, its incidence dramatically increases with increasing age. In the west, more than fifty percent of cancers occur beyond sixty-five years of age and demographically this population is increasing. According to estimates in the United States, within the next 30 years the absolute number of cancers occurring in persons ≥ 65 years old is expected to double, and the number of cancer patients ≥ 85 years old is expected to increase by more than four-fold between 2000 and 2050. Elderly cancer patients have a sixteen times greater risk of dying from cancer as compared to younger patients and thus contribute to a significant proportion of worldwide mortality.

Presently, elderly (persons above 65 years of age) comprise 5.5-7% of the total population of India. Life expectancy in India has doubled since independence and a 43% increase in the elderly population is projected by the year 2025. In India, 8 to 10 lakh new cases of cancer are detected every year. As a consequence of these demographic changes, a 280% increase in cancer is expected to occur by 2025. A further 220% increase in the incidence of cancer is expected due to increase in tobacco consumption. Hence physicians will be faced with more elderly patients with cancer than ever before (Table 1).

AGEING AND CANCER

Age is a risk factor for cancer. Patients are more prone to develop cancers at old age due to a variety of factors. Over their lifespan, tissues of older persons are exposed to serial stochastic genetic events involved in multi step carcinogenesis. People had been exposed to carcinogens over a prolonged period and there is accumulation of DNA adducts and mutations over time. The number of cells that would be susceptible to the effects of late stage carcinogens increases with age. The process of ageing involves genetic events similar to those occurring in early carcinogenesis. Reduced DNA repairing ability, genetic instability, decreased carcinogen metabolism and decreased immune surveillance at old age add to the increased cancer risk.

BIOLOGY OF CANCER IN ELDERLY-ARE CANCERS IN OLDER PATIENTS DIFFERENT?

The biology of cancer in elderly patients appears to be different to that in the younger population. Breast, lung and prostate cancer appear to have a more indolent course in the elderly. Immune senescence, age related changes in endocrine, nutritional, and wound-healing functions may contribute to the reduced tumor growth in these diseases.

In contrast, colorectal cancer, leukemia’s and lymphomas tend to have a more aggressive course in the elderly population. For example, acute myeloid leukemia (AML) in older age is associated with several poor risk biologic factors like antecedent myelodysplasia/secondary AML, poor risk cytogenetic features and high MDR expression. As a result, AML in elderly is poorly responsive to chemotherapy and has a shorter disease-free and overall survival.

WHY ELDERLY CANCER PATIENTS HAVE LESS SURVIVAL?

“As I give thought to the matter, I find four causes for the apparent misery of the old age: first, it withdraws us from active accomplishments; second, it renders the body less powerful; third, it deprives us of almost all forms of enjoyments; fourth, it stands not far from death.....”

- Marcus Tullius Cicero

The case of an elderly cancer patient presents significant challenges. In general, survival after cancer diagnosis declines as age increases. Several factors are responsible for the apparently poor survival of elderly cancer patients.

Suboptimal treatment

Cancer is frequently under-treated in elderly cancer patients. Population-based studies in the United States, Europe, and Canada have consistently identified old age as a barrier to access for therapy, including surgery, radiotherapy, and chemotherapy in cancer patients. Factors that are considered in offering cancer treatment are age, patient’s desire, the type and stage of the cancer, the potential curability of the cancer, performance status, comorbid factors, accessibility of treatment, social support and socioeconomic status. Such barriers are even more pronounced in India, where most patients do not have medical insurance.

Table 1: Comparison of population age groups

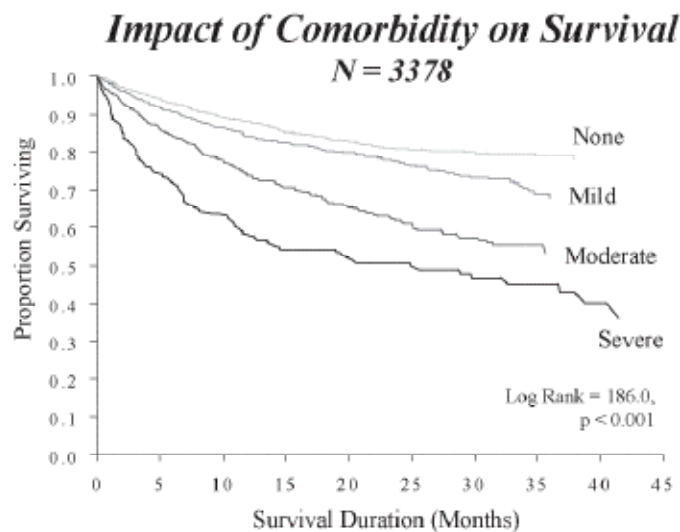
Age	Population in Developing Countries			Population in Developed Countries		
	1985	2010	Change %	1985	2010	Change %
<15	1,365	1,815	+33	260	248	-5
15-64	2,157	3,748	+74	780	868	+11
>65	155	330	+113	135	193	+43
All	3,677	5,893	+60	1,174	1,310	+12
Cancer cases	3.96	7.88	+90	3.66	5.04	+38

It is often considered that the prognosis of elderly patients with cancer is very poor. Elderly patients themselves are often reluctant to take treatment fearing that they might not be able to tolerate the treatment. It is more acceptable to people to die from malignancy than to risk toxicity. Even primary care physicians are sometimes reluctant to refer elder patients to cancer centers or oncologist. Often, family members also take less interest in the treatment of elderly cancer patients. Many of the cancer therapies are costly and as financial reserves are diminishing with old age, cost of treatment can also become a barrier to cancer treatment. As a consequence of these factors, very large number of older patients who can potentially benefit from treatment are not offered treatment. The fraction of such patients increases with increasing age.

In general, elderly patients tend to receive less aggressive therapy. For example, in a retrospective review of treatment of breast cancer patients aged ≥ 80 years, 12% of women had no treatment, 32% received tamoxifen only, 7% had breast-conserving surgery only, 33% had mastectomy, 14% had breast-conserving surgery plus adjuvant therapy, and 2% received miscellaneous treatments. Five-year specific breast cancer survival was 46%, 51%, 82%, and 90% for women with no treatment, tamoxifen alone, mastectomy, and breast-conserving surgery plus adjuvant treatment, respectively. In this study, only 47% of elderly women received standard treatment compared to the historical figure of 91% for women aged 50 to 79 years. Other similar studies have shown that older breast cancer patients are less likely to undergo breast conservation surgery. Postoperative radiation therapy is likely to be omitted in patients who have undergone this surgery. Suboptimal treatment administered due to advanced age is obvious in studies of other malignancies such as lung, colorectal, and lymphomas also.

This problem is widespread due to the prevailing misconception about the safety and feasibility of potential therapies. Elderly patients are perceived to be less able than younger patients to tolerate standard chemotherapy regimens because of their decreased hematopoietic reserves, the high prevalence of comorbidities, and the greater risk of toxicity. Physicians often tend to compromise on the dose of chemotherapeutic drugs in elderly patients. This results in inferior outcomes.

Surgery is often considered to carry a prohibitive risk for morbidity and mortality in the elderly cancer patient. This so called increased mortality is actually due to factors other than tolerability in the elderly. Due to underutilization of screening, tumors are often diagnosed at an advanced stage. Such advanced

**Fig. 1:** Effect of co-morbidities on survival in cancer

tumors usually require more extensive (and often emergency) surgeries, which have high mortality.

Co-morbidities

Elderly are at greater risk of treatment complications if they also have certain co-morbidities. Comorbid illnesses have a complex interaction and may influence disease course, treatment related side effects and mortality. Older patients are at high risk for having cognitive impairment, depression, nutritional problems, falls and fractures. Patients are often receiving concomitant medications, which increases the risk of for drug-drug and drug-disease interaction (Fig. 1).

Poor tolerance to treatment

Complications of cytotoxic chemotherapy can be more common in older patients with impaired organ function reserve. The occurrence of myelosuppression, mucositis, cardiotoxicity, and neurotoxicity can complicate treatment. For example, in a CALGB Study, the incidence of cytosine arabinoside induced cerebellar ataxia was 10 times more in the elderly patients as compared to patients between 20-40 years of age. Prospective trials in older patients with lymphoma or solid tumors have also found age as a risk factor for chemotherapy-induced neutropenia and its complications. Anemia may be present because of the disease or its treatment, and, if left uncorrected, can alter drug activity and increase toxicity.

Toxicities are dependent on the type and dose-intensity of therapy, the type and stage of cancer, the underlying biology of the cancer, and differences in functional reserve of the different organ systems. Age-related physiologic changes that can increase the toxicity of chemotherapy are decreased renal, hepatic & bone marrow reserves, decreased ability to repair cell damage, progressive loss of body protein, and accumulation of body fat. Age related decline in organ function alters the pharmacokinetics of several chemotherapeutic agents. Mucosal atrophy and decrease in gastrointestinal motility, splanchnic blood flow and secretion of digestive enzymes leads to impaired absorption of drugs. Similarly changes in body composition in old age leads to decreased volume of distribution of more polar drugs while the

volume of distribution of lipid soluble drugs increases. This can lead to lower peak concentration and prolonged terminal half-life of drugs that might result in an increased toxicity. Changes in liver size, blood flow and metabolic enzymes often alters drug metabolism and the loss of renal mass and decline in glomerular function can lead to impaired excretion of drugs that are excreted by the kidneys.

Lack of appropriate therapeutic guidelines

Many treatment decisions can only be made appropriately when clinical trials addressing therapeutic dilemmas have been performed. What constitutes appropriate or optimal treatment for elderly patients with cancer is often not clear because they are underrepresented in most clinical trials. Although 61% of new cases of cancer occur among the elderly, recent studies indicate that the elderly comprise only 25% of participants in cancer clinical trials. A recent analysis by the Southwest Oncology Group (SWOG) of more than 16,000 clinical trial participants found that only 39% of the lung cancer subjects enrolled in SWOG trials between 1993 and 1996 were older than 65 years, whereas 66% of the lung cancer population in the United States is older than 65 years. Similarly, in a retrospective analysis of NCI data of 59,300 patients enrolled in 495 NCI-sponsored, cooperative group trials only 32% of participants in phase II and III clinical trials were elderly, compared with 61% of patients with incident cancers in the United States who are elderly. Interestingly, the degree of under-representation is more pronounced in trials for early-stage cancers than in trials for late-stage cancers. This could probably be due to the simple fact that elderly cancers are diagnosed at an advanced stage.

CAN THE SURVIVAL OF ELDERLY CANCER PATIENTS BE IMPROVED?

The answer is YES! Elderly patients receive equal benefit from equal treatment.

Undertreatment in elderly patients with cancer is the primary reason for their poorer outcomes as compared to younger patients. Fit older patients must be treated with the same intensive approaches that are standard of care for younger patients. The results reported in randomized controlled clinical trials are consistent with the capability of older patients to exhibit overall response rate, event-free survival, and overall survival similar to those observed in their younger counterparts. For example, the mortality for elderly patients undergoing elective colorectal surgery is 2% in patients beyond 65 years of age, which is not significantly different from that in the younger patients. For elderly fit colorectal cancer patients, the five years survival is similar to younger patients. For patients with liver metastases from colorectal cancer, even liver resections can be safely performed in the elderly. In a study of such liver resections, morbidity, mortality ICU admission rates and long-term survival rates were similar in elderly and young patients. The median hospital stay was only one day longer in patients beyond 70 years of age as compared to patients below this age. Similar studies in elderly gastric cancer patients have also shown that the five-year survival for curatively resected patients is similar in younger and older patients.

Table 2: Comprehensive Geriatric Assessment – Score in various geriatric age groups

Age Group	< 75 yrs	75-84	> 85 yrs
ECOG PS 0-1	90%	80%	46%
ADL Independent	87%	80%	64%
IADL Independent	52%	45%	36%
GDS negative	20%	22%	18%

We have seen similar results at our hospital as well. Let us take the example of Non Small Cell Lung Cancer (NSCLC). Over the last ten years, the 1 year survival for advanced disease treated with platinum based chemotherapy, has increased from 10% to 50%. The overall RR with platinum doublet has become an impressive 40%. When results are compared between young adults and the elderly, treated with the low dose prolonged infusion gemcitabine and carboplatin combination, the outcome (and toxicity) is identical (Table 2). This highlights the fact that fit elderly will benefit as much as younger patients – when treated with the same dose intense regimen.

Treatment in elderly cancer patients still need to be individualized for optimal outcomes – but this is not different from young adults. All cancer therapies need to be adapted to the patient's health status and comorbid conditions. The aim is to offer the best chance of cure regardless of age. Hence it is mandatory that patients are informed about available treatment options, as well as the consequence of suboptimal treatment.

Managing cancer in older patients usually takes into consideration their shorter life expectancy. This is wrong. Life expectancy remains high even after the age of 80 years and if left untreated, the risk of death due to disease increases. The medial life expectancy for a person at 70, 80 and 85 years is 14, 8 and 5 years respectively. This is more than the expected five-year survival of many cancers.

Thus it should be clear that chronological age does not always predict the physiologic decline in an individual. Several studies have shown that otherwise-healthy elderly patients can obtain the same benefits from the same treatment as younger patients (e.g. in breast and lung cancer, giving the same treatment regimen and dose-intensity in older patients, results in no increased toxicity and similar survivals compared with those of younger patients).

To ensure proper patient selection, cancer chemotherapy needs to be tailored based on drug absorption, saturation kinetics, compliance, pharmacokinetics and pharmacodynamics changes. Careful attention to physiologic changes with age and appropriate dose adjustments for end organ dysfunction are necessary during treatment. A less toxic drug analogue should be used whenever possible.

The development of effective principles for the management of toxicity caused by anticancer drugs is therefore the cornerstone in providing elderly people the best chance of cure and survival. Several strategies are available. For example hematopoietic growth factors have been shown to reduce the incidence and severity of neutropenia and its complications in older patients. They permit the delivery of standard doses of chemotherapeutic

Table 3: Outcome of gemcitabine carboplatin doublet on overall response in advanced non small cell lung cancer – comparison between all ages and elderly patients

NSCLC – gemcitabine / carboplatin	All ages (range 32 - 76)	Age 60 + (range 60 – 76)
N=	34 (median age 57)	16 (median age 67)
CR+ PR = RR	2+ 17 = 19	1 + 8 = 9
SD	9	4
PD + incomplete Rx	4 + 2 = 6	2 + 1 = 3
Overall RR	55.88 %	56.25 %

agents, essential for outcome. Anemia should also be vigorously treated. Hemoglobin should be maintained at 12 gm/dL with the use of erythropoietin, iron & vitamin supplementation and blood transfusions, as required.

A number of agents with favorable efficacy and toxicity profiles in elderly patients have also been identified. The availability of oral anti cancer medication with broad spectrum of activity has permitted the delivery of chemotherapy in patients with poor performance status. Many of the recently approved drugs have an improved therapeutic index for the elderly and have a broad range of activity. These drugs can be effectively used in the management of solid tumors like lung, breast, ovary, colon, and prostate cancer. Use of three-dimensional conformal RT, intensity-modulated RT, utilization of non-platinum-containing chemotherapy regimens, and novel targeted therapies (e.g. monoclonal antibodies) should further reduce the treatment related toxicity.

The prevailing misconceptions regarding prognosis of elderly cancer patients should be addressed aggressively. Attitudes of patients, their families and primary care physicians towards cancer treatment need to be changed. As the initial decision-making step in the healthcare process, the primary care physicians play a vital role in the management. Patient education and physician CMEs regarding the existent therapeutic options and available resources should improve the survival of elderly patients.

A thorough evaluation of elderly cancer patients should be done prior to starting treatment includes assessment of disabilities, comorbidity and functional status in addition to assessment of tumor type and stage. Factors such as patients' life expectancy, functional reserve, social support, and personal preference should be taken into account while designing treatment. Comprehensive geriatric assessment (CGA) involves the medical, functional, affective, social, spiritual and environmental assessment. Medical assessment includes evaluation of nutrition, vision, hearing, continence, gait and cognition in addition to evaluation of performance status. The CGA is a useful tool for estimating life expectancy, tolerance to treatment and for identifying reversible factors that may interfere with cancer treatment (including depression, malnutrition, anemia, neutropenia, and lack of caregiver support). The CGA adds substantial information on the functional assessment of elderly cancer patients, including patients with a good PS. The information from a CGA can guide the prescription of potentially curative therapy, determine the best use of supportive care agents, and help identify frail patients for whom palliative care is the best option. The routine use of

a CGA can help reducing hospitalization, preserve functional independence, and prevent geriatric syndromes (Table 3).

A better understanding of drug activity and toxicity in older patients is necessary for developing guidelines for safe and effective treatment. Being able to predict which elderly patients are at greater risk of toxicity on the basis of pretreatment factors would be valuable, and there is a need for prospective trials to determine regimen- and patient-specific prognostic factors. Protocol exclusion criteria on the basis of organ-system abnormalities and functional status are associated with lower elderly participation in clinical trials. If protocol exclusion criteria are relaxed, the participation of elderly patients in cancer trials should increase. A better understanding of the attitudes of older patients toward cancer care and clinical trials will lead to more effective strategies about how best to remove barriers that result in the inequity of their cancer management. Basing our clinical practices on extrapolation of data from studies in young patients or on the small number of elderly patients participating in the larger cooperative group studies may be hazardous. Elderly patients may require interventions different from their younger counterparts and clinical trials can help elucidate this. Therefore there is an urgent need to perform separate studies that enroll patients who are older than 60 - 65 years. They are required to address the indications of cancer screening based on life expectancy and quality of life. More studies are needed to address the specific issues of pharmacology of anti cancer drugs in elderly patient, activity of new drugs and biologic anti cancer agents in elderly, short term and long term side effects of treatments and ways to improve early diagnosis and treatment.

FUTURE CHALLENGES

The changing healthcare needs of an increasingly aging population must address the unique factors operating in elderly patients. Planning for effective preventive measures and improvement of treatment in the elderly is imperative to meet the current and future quality cancer care needs.

Family caregivers play an essential role in caring for patients with cancer. The needs of older patients are diverse and may include assistance with medication, transportation for treatment, activities of daily living, and emotional support.

Stronger ties must be made between physicians, oncologists and other health care personnel to address the issues of prevention, early diagnosis, treatment and quality of life of elderly cancer patients. A national resource centre for geriatrics and integrated training in geriatric oncology should be a first step in this direction. USA already has a formal fellowship program in Geriatric Oncology – available at 14 centers and run by the American Society of Clinical Oncology.

“Ageing seems to be the only available way to have a long life”

- Daniel Francois Esprit Auber

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