TITLE: Biological aspects of aging that influence response to anticancer treatments

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ABSTRACT

Purpose of review

Cancer is a disease of older adults, where fitness and frailty are a continuum. This aspect poses unique challenges to the management of cancer in this population. In this article we review the biological aspects influencing the efficacy and safety of systemic anticancer treatments.

Recent findings

The organ function decline associated with the ageing process affects multiple systems, including liver, kidney, bone marrow, heart, muscles and central nervous system. These can have a significant impact on the pharmacokinetics and pharmacodynamics of systemic anticancer agents. Comorbidities also represent a key aspect to consider in decision-making. Renal disease, liver conditions and cardiovascular risk factors are prevalent in this age group and may impact the risk of adverse outcomes in this setting.

Summary

The systematic integration of geriatrics principles in the routine management of older adults with cancer is a unique opportunity to address the complexity of this population and is standard of care based on a wide range of benefits. This approach should be multidisciplinary and involve careful discussion with hospital pharmacists.

KEYWORDS

Geriatric oncology, ageing, organ function decline, comorbidities, systemic anticancer therapy

INTRODUCTION

Population ageing is a global phenomenon affecting high-, middle- and low-income countries alike.(1) Individuals aged 65 years and older are the fastest growing segment and are expected to represent 16% of the general population in 2050. On the other hand, cancer is a disease of older individuals due to a sharp increase in the incidence of most type of malignancies after the age of 60 years. Managing cancer in older adults is a routine task for oncologists as this specific group of patients accounts for 50 percent of the overall incidence and 70 percent of the overall mortality associated with tumours.(2, 3) The essential principles of managing cancer are similar in younger and older adults. However, older patients with cancer are a very heterogenous population with unique needs and problems and where chronological age alone provides little information on their fitness.(4) This uncertainty may pose additional challenges to decision-making and the optimal delivery of anticancer treatments.

In this review, we outline the biological aspects of aging that may influence the efficacy and safety of systemic anticancer treatments and potential solutions to maximise these outcomes in this population.

TEXT OF REVIEW

CHALLENGES OF MANAGING CANCER IN OLDER ADULTS

Gaps of evidence

Older patients are underrepresented in the clinical trials that define the standard of care in cancer treatment.(5, 6) Although chronologic age alone should not be an exclusion criterion for trial enrolment, it remains a significant source of disparities for this specific population.(7, 8) Barriers typically include concerns related to patients and physicians on potential benefits and toxicities, strict eligibility criteria, comorbidities and logistical aspects.(9)

Additionally, older patients enrolled in oncology clinical trials are usually fitter compared with those seen routinely in clinical practice, which limits the external validity of their findings and the applicability of guidelines and consensus recommendations in the real world.(10)

As a consequence, there is a significant lack of evidence applicable to guide the management of cancer in older individuals, although several strategies have been outlined in order to expand the evidence base valid for this population.(11) These include broadening study eligibility criteria, enhancing education of healthcare professionals, increasing the resources and personnel needed to recruit and retain older patients in trials, implementing geriatric assessments, and designing studies with meaningful endpoints for older adults.

Complexity of older patients with cancer: Expectation of older subjects towards cancer treatment

Chronological age alone does not fully depict the complexity of older patients with cancer and their unique needs. In this population, potential treatment toxicities, quality of life, estimated life expectancy, age-related organ function decline and competing risks of mortality and morbidity need to be carefully considered in the context of their preferences. In particular, quality of life considerations are crucial in this population.

Older adults might be as willing to receive anticancer therapies as their younger counterparts, while they are less keen on enduring potential treatment-related adverse events.(12) Although data on the impact of anticancer treatments on quality of life in this age group are limited, their potential impact should be carefully considered in the decision-making process.(13, 14)

Older individuals are a heterogeneous population where fitness and frailty are a continuum.(15) Consequently, treatment decisions should be informed by a comprehensive assessment of domains relevant to their well-being, such as comorbidities, polypharmacy, functional status, nutrition, cognitive function, social support, and psychological status,(16) in the context of predicted life expectancy and patients' wishes.

The gradual organ function decline and the increasing prevalence of comorbidities and geriatric syndromes seen with ageing may have significant impact on outcomes of anticancer treatments and hence represent two of the most relevant challenges of managing cancer in this age group.

IMPACT OF ORGAN FUNCTION DECLINE

Organ function decline in an older patient is not measurable only by age.(17, 18) The importance of considering the organ function for the older individual is vital when starting anticancer treatment and also when reviewing patients while on treatment (Table 1). The response to the anticancer therapy and any manifestations of side-effects may be multifactorial.

Pharmacokinetics changes

Overall, the body processing of drugs is changed with aging. Therefore, pharmacists should be routinely involved in the care of older patients with cancer. Table 2 outlines the key changes associated with aging that may affect pharmacokinetics and pharmacodynamics of anticancer agents, along with the relevant assessment and potential solutions. The most important changes occur in the metabolism and the

excretion of the drugs due to the liver and renal changes with aging.(19, 20) The distribution of drugs between the lipid and water compartments is also altered due to the body composition changes with aging (increased adipose tissue, decreased lean body mass). The absorption of the drugs is hardly affected.

The liver is largely able to regenerate and aging, without other comorbidities, would not usually lead to severe hepatic dysfunction. The major liver functions are to detoxify the blood, metabolise carbohydrates and lipids, synthesis proteins and secrete bile. With any reduced function of the liver there may be implications for drug metabolism, elimination and risk of drug toxicities. Gastrointestinal changes, with reduced acid secretion and gut motility may impact of drug absorption. Renal function decline with age is a common issue in the elderly population. Decreased glomerular filtration rate can reduce drug excretion and increase toxicities. Older patients will be particularly at risk of issues with drugs affecting the cardiac function due to co-morbidities such as hypertension or coronary-artery disease and reduced cardiac reserve.(21) The physiology of aging means that the bone marrow reserve may be reduced prior to receiving anticancer treatment and cause prolonged neutropenia or thrombocytopenia.(17) Muscle wastage is characteristic of cachexia in advanced cancers but sarcopenia in the elderly also causes complications in earlier stages of the disease. Sarcopenia is related to reduced functionality and increase risk of falls, and early intervention helps to reduce adverse outcomes.(22) Decline in the neurological function may impact on compliance with anticancer therapies and increase the risk of CNS toxicities from treatments or supportive care.(17)

IMPACT OF COMORBIDITIES

Comorbidities are a key domain to evaluate for older patients being considered for systemic anticancer therapy.(23) In case of normal renal function and no significant comorbidities, most systemic agents can be given in standard doses. However, in case of comorbid conditions there may be an increased susceptibility to complications and dose adjustments are often required.

Renal dysfunction

Systemic agents with primary renal excretion should be used carefully in older patients because of the high incidence of occult renal impairment.(24, 25) These include cytotoxic agents (alkylating, antimetabolites, antimicrotubule, antitumour antibiotics, platinum compounds, immunomodulatory and proteasome inhibitors) and molecularly targeted agents.(26) Two large observational studies found that half of patients with cancer had an estimated glomerular filtration rate (GFR) of <90 mL/min/1.73m^2 along with a prevalence of stage 3 and 4 chronic kidney disease (CKD) of 12 and <1 percent;(27, 28) also, potentially nephrotoxic agents were used in up to 80 percent of chemotherapy sessions. Cancer patients with CKD may have increased risk of mortality which vary based on tumour type.(29)

Dose adjustments may still ensure adequate disease outcomes whilst preventing excess toxicity. For example, a study comparing different chemotherapy regimens for early-stage breast cancer including either doxorubicin plus cyclophosphamide, cyclophosphamide plus methotrexate plus fluorouracil or capecitabine in patients aged 65 years and older did not document any association between pre-treatment renal function and efficacy and safety.(30)

Several conditions can enhance renal dysfunction and contribute to the nephrotoxic potential of antineoplastic agents. These include: intravascular volume depletion due to external losses of fluid sequestration as seen in case of ascites or oedema; concomitant use of nephrotoxic drugs (such as antibiotics, nonsteroidal anti-inflammatory agents and proton pump inhibitors) or radiographic ionic contrast media; urinary tract obstruction due to the tumour; and intrinsic idiopathic renal disease associated with ageing, other comorbidities, or the tumour itself.

The presence of terminal renal disease requiring dialysis is also a particular challenge as the details of drug elimination and metabolism are not fully known in this scenario.(31) In general, dose reductions may be needed to avoid overexposure and drug toxicity and drug clearance by dialysis should be considered for appropriate timing of chemotherapy in order to avoid drug removal and loss of efficacy.(32)

The prevalence of an elevated serum creatinine is <10 percent in cancer patients but the prevalence of a reduced GFR is relatively high (50-53 percent).(27, 28) In older

patients, renal function should be assessed at least by calculation of creatinine clearance.(25) The estimation of GFR and the evaluation of clinical signs of drug toxicity should be considered for the purposes of dose adjustments. Although a creatinine clearance calculation based upon a 24-hour collection of urine is impractical and subject to errors, the use of bedside formulae such as the Cockroft-Gault(33), Modification of Diet in Renal Disease(34) and Chronic Kidney Disease Epidemiology Collaboration equations(35) based upon a stable serum creatinine concentration may be useful.

Liver disease

Moderate and severe hepatic dysfunction may influence the metabolism or excretion of systemic agents normally handled by the liver and increase the risk of adverse outcomes. This is relevant for the management of patients requiring specific cytotoxics, such as alkylating drugs, nitrosoureas, antimetabolites, antitumour antibiotics, tubulin-acting drugs, and targeted agents. Older patients with pre-existing liver disease should undergo a full diagnostic workup prior to chemotherapy to investigate its causes and severity and the management of coexisting conditions should be optimised to reduce the risk of anticancer therapy toxicities. Guidelines on dose adjustments in this setting are empirical as derived from small studies on the pharmacokinetics of anticancer agents.(36) Nonetheless, comprehensive resources such as LiverTox are available online on this topic.(37)

Hepatitis B (HBV) and C (HCV) infections are common conditions that may be exacerbated or reactivated with the use of cytotoxics. Interestingly, a substantial proportion of patients are unaware of their viral infection at the time of cancer diagnosis.(38) Pre-treatment viral load may influence survival and the incidence of severe hepatitis on chemotherapy for patients with HBV infection.(39) The risk of significant HBV reactivation is relevant for patients being considered for myelosuppressive agents such as anti-CD20 therapies and prophylactic anti-viral therapy may be appropriate in this setting. The risk of re-activation on less myelosuppressive agents used for solid tumours is less established and ranging from 4 to 68 percent.(40, 41) The American Society of Clinical Oncology currently recommends universal HBV screening for all patients suitable for cytotoxic

chemotherapy, immunotherapy, or molecularly targeted therapy, using hepatitis B surface antigen (HbSAg), hepatitis B core antibody (anti-HBc), total immunoglobulin (Ig) or IgG, and antibody to hepatitis B surface antigen (anti-HBs).(42)

HCV reactivation seems less common and the relationship with myelosuppressive chemotherapy is less clear.(43) However, the presence of pre-existing decompensated liver disease is critical to determine the risk of liver function derangement in patients with HCV undergoing treatment for haematological malignancies.(44) Therefore, clinicians should also consider testing for chronic HCV infection prior to starting immunosuppressive treatments.

Cardiac disease

Pre-existing occult cardiac disease is more prevalent in older patients compare with their younger counterparts(45) and it can increase the risk of heart failure on anthracyclines and trastuzumab, or coronary heart disease on fluoropyrimidines. A large registry data analysis of patients with diffuse B-cell non-Hodgkin lymphoma documented that the risk of heart failure increased by 29 percent in patients aged 65 years and older receiving doxorubicin and especially in those with a history of hypertension.(46)

Cardiovascular disorders involving a left ventricular ejection fraction (LVEF) ≤50 percent and hypertension and risk factors including older age, obesity, diabetes, smoking and hyperlipidaemia are associated with a higher risk of cardiac toxicity on anthracyclines.(47) This risk may be exacerbated by the use of radiotherapy involving the cardiac silhouette and trastuzumab. The cumulative anthracycline exposure is crucial to determine the risk of LVEF decline, the incidence of heart failure and cardiac mortality.(48) Obesity was also a key predictor of the risk of cardiac dysfunction in a meta-analysis of 15 trials of anthracyclines with or without trastuzumab for breast cancer.(47)

On agents targeting the human epidermal growth factor receptor 2 (HER2), older age, high body mass index, anti-hypertensive therapy, diabetes and use of anthracyclines

are risk factors for cardiac toxicity,(49-52) whereas valvular and cardiac heart disease do not significantly increase this risk.

Patients receiving fluoropyrimidines have higher chances of cardiac adverse outcomes in case of underlying heart disease, although findings may be conflicting.(53) Moreover, most cases of cardiotoxicity occur in patients without history of cardiac disease.(54) Data are conflicting also regarding the impact of age,(55, 56) concomitant chemotherapy agents(53) and radiotherapy.(56)

The risk of cardiac toxicity needs to be balanced against the benefit of anticancer treatment and in the context of novel approaches to prevent and manage cardiotoxicity.(57) Assessing the baseline risk on clinical history and cardiac examination is mandatory for older patients being considered for potentially cardiotoxic systemic anticancer agents. Some clinicians may also find it helpful to use electrocardiograms. Despite these approaches having limited ability to predict cardiac toxicity, they may help identify patients requiring optimisation of existing cardiovascular conditions. Baseline cardiac imaging may also be considered for patients suitable for anthracyclines or anti-HER2 therapy and may take the form of echocardiography, cardiac magnetic resonance or radionuclide ventriculography. Some experts suggests assessing also the global longitudinal strain,(58) troponin(59) and natriuretic peptide.(60) Cardiac risk score have also been developed to predict cardiotoxicity although independent validation is needed.(51, 61, 62)

Cognitive dysfunction

It is now well established that aging did not result in significant cognitive impairment, but the cognitive reserve, the speed of task execution and new task learning are somehow decreased.(63) This physiological aging brain function, even more when it has latent undiagnosed more important cognitive alterations like Mild cognitive impairment (MCI) may influence the response to anti-cancer drugs.(64)

It is now well-established that the chemotherapy induced cognitive impairment affect many patients receiving anti-cancer agents such as antimetabolites, alkylating agents, tyrosine kinase and microtubule inhibitors. Up to 70% of chemotherapy treated cancer survivors experience cognitive deficits at any moment of their treatment affecting their quality of life. The main affected cognitive domains are memory, attention, learning,

executive functions somehow impacting some of those already changed with aging.(65) This means that all older subjects should have a cognitive evaluation before any chemotherapeutic agents to avoid further impairment if any.

CONCLUSIONS

Benefits of integrated oncogeriatric care

When managing older patients with cancer, there is a need to identify those who are apparently frail but likely to benefit from and tolerate standard therapy, as well as those older patients who are seemingly fit yet at risk of experiencing undue side effects and require modified anticancer treatment plans. A comprehensive geriatric assessment (CGA) is a multidisciplinary diagnostic process evaluating age-related concerns that may help evaluate and achieve the delicate balance between pros and cons of systemic treatment decisions (Table 3).

CGA is now recommended as a standard of care for older patients with cancer by international consensus guidelines on the basis of a wide range of benefits.(18, 23, 66, 67) These include the prediction of adverse outcomes including functional decline on anticancer treatments, a better estimation of survival, the detection of issues neglected by routine assessments, and improved mental health, pain control and well-being. More recently, four randomised clinical trials have demonstrated that integrated oncogeriatric care reduces the incidence of severe toxicities, treatment discontinuation and hospital admissions on chemotherapy, improves quality of life, increases the completion of advanced directives, and reduce the risk of intensive care admissions and re-admission following surgery.(68-71) In this context, multidisciplinary care is recommended along with the routine involvement of pharmacists in anticancer therapeutic decisions for older patients.

KEY POINTS

- Older patients are a heterogeneous population where chronological age alone provides little information about systemic anticancer treatment outcomes
- Age-related organ function decline may have a significant impact on the pharmacokinetics and pharmacodynamics of most systemic anticancer agents
- Comorbidities play a significant role in determining tolerance to systemic treatments
- Ongoing discussion with hospital pharmacists is key when managing older patients with cancer within a multidisciplinary setting
- Geriatric assessments are standard of care when managing cancer in older individuals in view of a broad range of benefits

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Conflicts of interest

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TABLES AND FIGURES

Table 1 – Impact of organ function decline on outcomes of commonly used systemic anticancer agents.

Drug class	Organ system	Clinical considerations
Anthracyclines e.g. epirubicin	Cardiac	Maximum cumulative lifetime dosing – may be limited either due to reduced baseline cardiac function, or prior anthracycline exposure.
	Hepatic	Major route of elimination via the hepatobiliary system. Consider dose reductions.
Vinca-alkaloids e.g. vinorelbine	Hepatic/GI	Vinorelbine may be less neurotoxic than other vinca-alkaloids but it is metabolised in the liver and metabolites excreted in faeces. Any reduction in hepatitis or gastric function may increase toxicities.
Antimetabolite e.g. capecitabine	Hepatic	Although upfront dose reduction may not be required for capecitabine due to hepatic impairment, older patients (≥60 years) have shown to have increased grade 3 and 4 toxicities.
	Renal	Capecitabine (and its metabolites) are principally renally excreted and renal impairment requires dose adjustments.
Alkylating drugs e.g. cyclophosphamide	Hepatic	Hepatic impairment may decrease the activation of cyclophosphamide and lead to reduced efficacy.
Platinums e.g. carboplatin	Bone marrow	Decreased bone marrow reserve and enhanced risk of myelosuppression – consider prophylactic colony-stimulating factors if dose intensity needs to be maintained.
	Renal	Major route of clearance via the kidneys and delayed excretion may enhance toxicities.
Monoclonal antibodies e.g. trastuzumab	Cardiac	Reduced baseline cardiac function – consider closer monitoring/specialist cardio-oncology input for patients on HER-2 directed therapies.
Targeted therapies/small molecules e.g. cyclin-dependent kinase (CDK) 4/6 inhibitors	Bone marrow	Decreased bone marrow reserve and enhanced risk of myelosuppression. No evidence for use of colony-stimulating factors with CDK4/6 inhibitors.
	Cardiac	Ribocicilb has a specific ECG monitoring requirement due to risk of QT interval prolongation.
	Hepatic	May be metabolised in the liver and to consider upfront dose reductions to prevent adverse drug events.
	Renal	Abemaciclib may increase serum creatinine without reducing GFR and this could be wrongly interpreted as renal impairment in an older patient.
Immunotherapies e.g. pembrolizumab	Multi-organ	Higher incidence of grade 3 and above toxicities in older patients that may impact on quality of life and performance status. Treatment with immune checkpoint inhibitors appear to show better tolerability than cytotoxic therapies.
Endocrine therapy e.g. fulvestrant	Muscle	The administration is via an intramuscular injection and may be difficult in patients with sarcopenia.
Supportive care e.g. metoclopramide	Neurological	Metoclopramide is known to cause dystonic effects, and this may be irreversible with prolonged use, especially in the very old.
Supportive care e.g. dexamethasone	Multi-organ	Common adverse effects of steroids may be associated more serious effects, especially if used for prolonged periods - risk of diabetes, osteoporosis, hypertension, hypokalaemia and close clinical supervision is needed.

Table 2 – Suggestions for the assessment and management of key organ function changes associated with aging.

Organ system	Aging related changes	Implications	Assessments	Management
Liver	Hepatic volume decline Hepatic blood flow decline	Decreased drug metabolism Decreased drug elimination Increased treatment toxicities	Liver function tests	Anticancer therapy dose adjustment Optimising concurrent medications
Kidney	Decreased glomerular filtration rate	Volume depletion Decreased drug elimination Increased treatment toxicities	Renal function tests Glomerular filtration rate Creatinine clearance	Anticancer therapy dose adjustment Adequate fluid intake Optimising concurrent medications
Muscles	Sarcopenia	Decreased mobility Impaired functional status Increased risk of falls	History Physical examination Imaging	Exercise Diet and adequate protein intake
Bone marrow	Decreased bone marrow reserve	Increased treatment toxicities	Full blood count	Anticancer therapy dose adjustment Blood products Iron supplementation Vitamin B12 supplementation Folate supplementation Erythropoietin
Bone	Osteopenia and osteoporosis	Increased risk of fractures Decrease mobility Impaired functional status	Dual energy X-ray absorptiometry	Diet Exercise Cessation of smoking Calcium supplementation Vitamin D supplementation Antiresorptive agents
Central nervous system	Neuron loss Reduced brain blood flow	Impaired cognition and dementia Increase risk of falls Increased susceptibility to benzodiazepines	History Physical examination Cognitive testing Screening for depression Vitamin B12 levels Thyroid function Neuroimaging	Vitamin B12 supplementation Thyroxine Behavioural interventions Pharmacologic interventions
Gastrointestinal	Poor motility Decreased acid production	Poor drug absorption	History Physical examination Stool tests for fat malabsorption Endoscopy Breath tests Small bowel/pancreatic imaging	LIfestyle modifications Dietary modifications (fibers) Bulk forming and osmotic laxatives Stool softeners
Cardiovascular	Decrease ventricular compliance Diastolic dysfunction Increased wall thickening	Increase risk with cardiotoxic drugs Higher risk of arrhythmias	Echocardiograms (left ventricular ejection fraction and global longitudinal strain) Multigated acquisition scan Troponin Plasma brain natriuretic peptide or N-terminal pro-brain natriuretic peptide	Anticancer therapy dose adjustment Use of alternative non-cardiotoxic agents
Lungs	Decreased lung compliance Decreased sensitivity of the respiratory center Decreased mucociliary function	Decreased pulmonary capacity Higher risk of pulmonary infections Limitation on options for lung surgery/radiation	Pulmonary function tests (spirometry, peak expiratory flow, lung volumes, diffusing capacity, pulse oximetry, arterial blood gases) Chest radiography Computer tomography	Pulmonary rehabilitation Physical activity

Table 3 – Comprehensive geriatric assessment tools.

Domain	Tool	Time to administer	Abnormal score
Demographic and social status	• Conditions of living, marital status, educational level, financial resources, social activities, family support • Identification of the caregiver and burden (Zarit Burden Interview)	10 min 15-20 min	 >20
Comorbidities	• Charlson comorbidity index(72) • CIRS(73) • CIRS-G(74) • Physical Health Section (subscale of OARS)(75) • Simplified comorbidity score(76)	2 min	
Polypharmacy	• Beers criteria(77) • STOPP and START criteria(78)		
Functional status	• ADL (Katz index)(79) • IADL (Lawton scale)(80) • Visual and/or hearing impairment, regardless of use of glasses or hearing aids • Mobility problem (requiring help or use of walking aid) • Timed Get Up and Go(81) • Hand grip strength • Walking problems, gait assessment, and gait speed(82, 83) • Self-reported no. of falls (within different time frames)		<6 <8 ≥14s <1m/s
Cognition	• Mini Mental State Examination(84, 85) • Montreal Cognitive Assessment(86, 87) • Clock-drawing test(88) • Blessed Orientation-Memory-Concentration Test(87) • Mini-cog(89)	10-15 min	<24 <26 <5 >4 <4
Mood	• Geriatric Depression Scale (mini GDS, GDS-15, GDS-30)(90, 91) • Hospital Anxiety and Depression Scale(92, 93) • Distress thermometer	15 min	Mini GDS: <1; GDS-15: >5; GDS-30: >10 >7
Nutrition	• Body-mass index (weight and height) • Weight loss (unintentional loss in 3 or 6 months) • Mini Nutritional Assessment(94, 95) • Dentition		<23 <24
Fatigue	MOB-T(96)		
Geriatric syndromes(67)	• Dementia • Delirium • Incontinence (faecal and/or urinary) • Osteoporosis or spontaneous fractures • Neglect or abuse • Failure to thrive • Pressure ulcer • Sarcopenia		