

Cardiotoxicity in the Elderly

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14.1 Introduction

The age distribution of population greatly affects its burden of disease and disability, including cancer incidence and mortality. Cancer is now the leading cause of death. Actually, cancer cases reported over the world have doubled in the past 25 years and could even triple by 2030. In fact, the elderly population is rapidly increasing, in Europe 15 % of the population is elderly, and 55 % of cancers are in this group of age [1, 2]. Therefore, age is an important risk factor for cancer. And, as we know, the cancer is forty times higher after 65 years, than when you are aged between 20 and 44 years. Older adults with cancer have different needs than younger adults with the disease. So treatment for older adults needs to consider many issues because they have unique needs by reason of their complex medical histories, numerous drugs taking, their social situations, possible problems with cognitive dysfunction related to age, and general diminution of organ function that occurs naturally in the older population. In contradiction with the fact that the risk of cancer increases with age, there is little interest in their clinical problem. In fact, clinical trial guidelines for treatment of cancer were mainly based on assessment for young age and rarely in elders. That disparity is demonstrated by a low percentage of research in this area. But now there's a big shift in the way oncologists approach treatment for elderly, and oncology management began to raise the consciousness that age was not a contraindication per se and starting in the mid-1980s the need of data and information [3, 4]. Ageing is associated with the decline in organ function that occurs over time and even in the eventual presence of injury, illness or poor lifestyle choices (e.g. unhealthy diet, lack of exercise, substance abuse). Initially, the changes in organ function do not affect baseline function; the first manifestations are a reduced capacity of each organ to maintain homeostasis under stress (e.g. illness, like cancer and, injury, like chemotherapy). The cardiovascular, renal and central nervous systems are usually the most vulnerable (the weakest links) [5].

14.2 Characteristics of Elderly People

The ageing process is characterised, for both acute and chronic diseases, by a progressive decline in physical and cognitive functioning whose underlying causes are only partially understood. As a consequence, one of the most characteristic aspects of ageing is the great variability from person to person: some persons maintain their physical and cognitive abilities throughout a long life (successful ageing), while others lose these abilities rather early in adult life. In a very small subgroup of individuals, the functional status even appears to improve over time. The basis for this heterogeneity is largely unknown and probably is affected by the interaction of genetic, environmental, functional, social and psychological factors that make up the individual ageing process [5].

Key Points: Characteristics of Elderly People

- Having multi-morbidity or co-morbidity
- Having unusual presentations of illness
- Experiencing organ physiologic change
- Being functional or psychological a risk of dependency
- Having frailty syndrome

14.3 Evaluating Older Patients for Screening Purpose: The Comprehensive Geriatric Assessment (CGA)

Among the elderly patients, to identify the best candidate to receive potential cardiotoxicity chemotherapy assumes a crucial role [6].

As age from a clinical perspective is highly heterogeneous and poorly reflected by chronological age, the clinical evaluation of the older person is influenced by several factors and is a **key step** in the clinical decision process. A geriatric consultation provides a variety of relevant information and enables the healthcare team to manage the complexity of health care in the elderly; this process is named **Comprehensive Geriatric Assessment (CGA)**.

CGA is defined as a multidimensional, often interdisciplinary, diagnostic process aimed at determining the medical, psychological and functional capabilities of elderly persons in order to develop an overall plan for treatment and long-term follow-up. It differs from the standard medical evaluation because (1) it focuses on frail elderly people with their complex problems, (2) it puts emphasis on the functional status and on their quality of life and (3) it benefits from the use of an interdisciplinary team. In the geriatric setting, several studies have supported the effectiveness of CGA in improving functional status, reducing hospitalisation, decreasing medical costs and prolonging survival. The meta-analysis by Stuck and colleagues showed a positive effect of the CGA, and the authors recommended its use within interdisciplinary units [7, 8].

Aim of CGA is the study of the complexity of many aspects of old age and the application of knowledge related to the biological, biomedical, behavioural and social aspects of ageing to diagnosis, treatment and care of older persons.

The onco-geriatric approach is specifically targeted towards patients with multiple, interacting problems brought on by disease or ageing and resulting in a progressive reduction of reserve of multiple organ systems, disability (i.e. functional impairment and dependency), co-morbidity, frailty and geriatric syndromes. Such patients are not simply old, but are “geriatric” patients because of interacting psychosocial and physical problems. In addition, diseases in the elderly may appear with atypical signs and symptoms, a silent presentation may occur, and they are extremely susceptible to iatrogenic disease. Chronic diseases are common and their contribution makes the picture more complex [9–11].

As a consequence, the health status of old persons cannot be evaluated by merely describing the single disease and/or by measuring the response or survival after treatment. Conversely, it is necessary to conduct a more comprehensive investigation of the “functional status” of the aged person. The assessment of the functional status is defined as the measurement of a patient’s ability to complete functional tasks, which range from simple self-care in activities of daily living (ADL) [12] to more complex instrumental activities of daily living (IADL) [13], and fulfil social roles. ADL includes feeding, grooming, transferring and toileting. IADL includes shopping, managing finances, housekeeping, laundry, meal preparation, ability to use transportation and telephone and ability to take medications. Independence, or the degree of dependence in the ADL and IADL scales, determines whether an older person can eventually live alone without a caregiver. As for social roles, these include the ability to use transportation, the ability of requiring help in cases of urgent need and the ability of living in an interpersonal context. Each impairment in the physical, social or psychological dimension which gives rise to functional limitations is defined as disability.

In the early 1990s, Monfardini and colleagues designed and validated a comprehensive geriatric assessment instrument tailored on oncological setting [14]. Such instrument included an evaluation of functional status (ADL, IADL), co-morbidity condition (Cumulative Illness Rating Scale CIRS) [15], cognitive function (Mini-mental state evaluation) [16], depressive symptoms [17], polypharmacy and nutrition.

Such “geriatric” approach may help in the management of older individuals with cancer in at least three areas: detection of frailty, treatment of unsuspected conditions and to design personalised treatment plan [11, 18].

Key Points

In the case of the older cancer patient, the CGA presents the following advantages:

- Estimate of life expectancy
- Estimate of functional reserve and tolerance of chemotherapy
- Recognition of reversible co-morbidity conditions that may interfere with cancer treatment.
- Recognition of special social economic needs that may interfere with cancer treatment.
- Management of nutrition and medications.

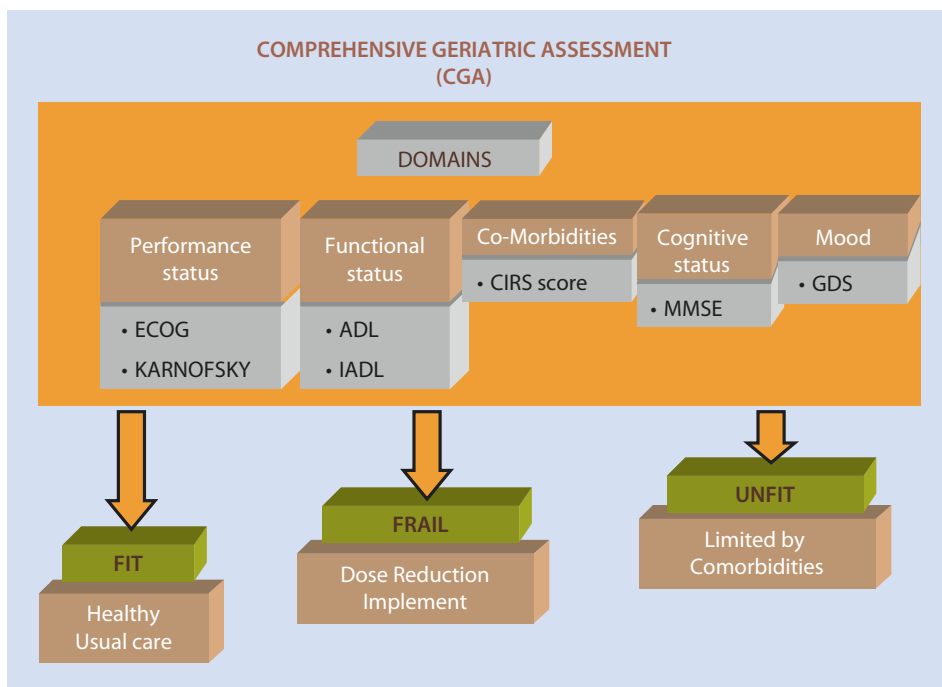
The SIOG included CGA in the guidelines for the management of elderly cancer patients: the main recommendation was that these scales are applied to all elderly cancer patients regardless of age to estimate functional status in order to determine a treatment course, assess eligibility for clinical trials and predict treatment toxicity [19] (■ Table 14.1).

The further evolution on application of such approach was to use the Geriatric Multidimensional Assessment as a milestone in screening process and in decision-making. Oncologists should be able to intervene and to target interventions by choosing between aggressive or palliative treatments and to prevent toxicity. To assess global health and age-related problem recognition could lead to a stratification of elderly cancer patients for entering optimal treatment strategies and/or clinical trials. Usually according to CGA elderly cancer patients evaluated to treatment course are classified in three risk groups: fit, unfit and frail patients (■ Fig. 14.1).

Table 14.1 SIOG recommendations for the management of anthracyclines' cardiovascular risk. Reproduced with permission from [19]

Recommendations	Proposal
Rigorous screening to exclude patients at unacceptably high cardiac risk (level 1a)	Comprehensive patient history: Current signs or history of CHF Cardiovascular co-morbidity (i.e. hypertension, diabetes or coronary artery disease) Prior exposure to anthracyclines for this or previous malignancy (level 1a)
Not exceeding the recommended upper cumulative dose (level 1a)	Reduction in maximum cumulative dose (level 5)
Use of less cardiotoxic therapy (level 1a)	Use of continuous infusion (level 1a) Epirubicin (level 1a) Dexrazoxane (level 1b, Elderly: level 5) Liposomal anthracycline formulations (level 1b, elderly: level 5) Sequential administration of conventional anthracyclines and trastuzumab in HER2-positive breast cancer (level 1b, elderly: level 5)
Regular monitoring of cardiac function, signs and symptoms (level 1a)	Measure of LVEF by ultrasound (preferred, level 5) or MUGA scan, every two to three cycles of anthracyclines (level 1a) Special attention needed if drop in LVEF exceeds 10%, even if remaining within normal range (level 5) Long-term follow-up (level 1a)
Cardiovascular risk reduction interventions (level 1a)	Early management of dysfunction (level 1a) Lifestyle modifications (i.e. smoking cessation, regular exercise, weight loss where appropriate) (level 1a) Beta blockers and ACE inhibitors (level 1a) Reduced lipid levels (level 1a)

CHF congestive heart failure, *MUGA* multiple uptake gated acquisition, *ACE* angiotensin-converting enzyme



■ Fig. 14.1 Aspects of comprehensive geriatric assessment

14.4 The Frail Cancer Patient: Definition and Identification

A key step in the patient evaluation in the onco-geriatric setting is the definition and identification of frailty that represents a major issue in clinical geriatrics. Although the term frailty has been increasingly used since the 1980s in the medical literature, its actual meaning is still not well defined.

Different authors emphasize different aspects of frailty [5], and frailty includes the following notions:

- Being at a substantial risk of dependency and other adverse health outcomes
- Experiencing the loss of “physiological reserves”
- Having complex medical and psycho-social problems

In the oncological setting, Balducci firstly defined frailty condition as to be over 80 years old, to have some ADL disability or to be affected by more of three co-morbidities or by a geriatric syndrome [4]. Frailty is a reversible condition characterised by a high degree of susceptibility to external changes that require adaptation and compensation. On these bases, when cancer is the “external change” the main objective of frail detection is to adopt compensatory strategies acting at different levels. For instance, the cellular biology level (e.g. growth factors, erythropoietin), the physiologic level (e.g. supportive therapies) and the metabolic pathways (nutritional support) interplay between functional status and social behaviours. With regard to social behaviours, a particular role is played by caregivers whose presence assures adherence to therapeutic plans.

For all these reasons, the effects of ageing must be taken into account during diagnosis and treatment of the elderly [20].

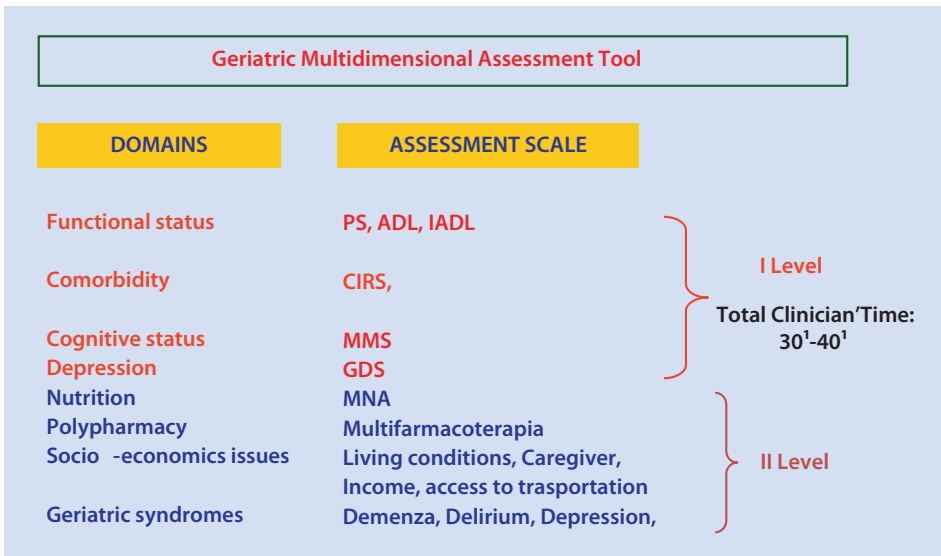
Clinicians should:

- Assess older people according to multidimensional approach by means of validated geriatric assessment tool.

Clinicians should not:

- Mistake pure ageing for disease (e.g. slow information retrieval is not dementia)
- Mistake disease for ageing (e.g. ascribe debilitating arthritis, tremor or dementia to old age)
- Ignore the increased risk of adverse drug effects on weak-link systems stressed by illness
- Forget that the elderly often have multiple underlying disorders (e.g. hypertension, diabetes, atherosclerosis) that accelerate the potential for harm

In addition, clinicians should be alert for diseases that are much more common among the elderly (e.g. diastolic heart failure, Alzheimer disease, incontinence, normal pressure hydrocephalus). This approach enables clinicians to better understand and manage the complexity of the diseases that often coexist in older patients (▣ Fig. 14.2).



▣ Fig. 14.2 First and second level assessment of geriatric patients

The unmodifiable effects of ageing may be less dramatic than thought, and healthier, more vigorous ageing may be possible for many people. Today, people >65 are in better health than their ancestors and remain healthier longer. Because health has improved, decline tends to be most dramatic in the oldest old.

14.5 Selected Physiologic Age-Related Changes

Evaluation of the elderly usually differs from a standard medical evaluation. For elderly patients, especially those who are very old or frail, history taking and physical examination may have to be done at different times, and physical examination may require two sessions because patients become fatigued.

The elderly also have different, often more complicated healthcare problems, such as multiple disorders, which may require use of many drugs (sometimes called polypharmacy) and thus greater likelihood of a high-risk drug being prescribed.

14.5.1 Multi-morbidity and Co-morbidity

Diseases interact with pure ageing effects to cause geriatric-specific complications, particularly in the weak-link systems—even when those organs are not the primary ones affected by a disease. Typical examples are delirium complicating pneumonia or UTIs and the falls, dizziness, syncope and weight loss that often accompany many minor illnesses in the elderly [21].

14.5.2 Unusual Presentations of Illness in the Elderly

In the elderly, many common conditions can exist without their characteristic features. Instead, the elderly may have ≥ 1 non-specific geriatric syndromes (e.g. delirium, dizziness, syncope, falling, weight loss, incontinence). These syndromes result from multiple disorders and impairments; nonetheless, patients may improve when only some of the precipitating factors are corrected. An even better strategy is to identify risk factors for these syndromes and correct as many as possible, thus reducing the likelihood of the syndrome's developing at all.

Although virtually any illness or drug intoxication can cause geriatric syndromes, the following disorders are especially likely to trigger one or more of them, sometimes instead of causing the typical symptoms and signs:

- **Heart failure** may cause confusion, agitation, anorexia, weakness, insomnia, fatigue, weight loss or lethargy; patients may not report dyspnoea. Orthopnoea may cause nocturnal agitation in patients who also have dementia. Peripheral oedema is less specific as a sign of heart failure in elderly than in younger patients. In bed-bound patients, oedema may occur in the sacral area rather than in the lower extremities.
- **Hyperparathyroidism** may cause non-specific symptoms: fatigue, cognitive dysfunction, emotional instability, anorexia, constipation and hypertension. Characteristic symptoms are often absent.

- **Hyperthyroidism** may not cause the characteristic signs (e.g. eye signs, enlarged thyroid gland). Instead, symptoms and signs may be subtle and may include tachycardia, weight loss, fatigue, weakness, palpitations, tremor, atrial fibrillation and heart failure. Patients may appear apathetic rather than hyperkinetic.
- **Hypothyroidism** may manifest subtly in elderly patients. The most common symptoms are non-specific (e.g. fatigue, weakness, falling). Anorexia, weight loss and arthralgias may occur. Cold intolerance, weight gain, depression, paraesthesias, hair loss and muscle cramps are less common than among younger patients; cognitive dysfunction is more common. The most specific sign—delayed tendon reflex relaxation—may not be detectable in elderly patients because of decreased amplitude or absent reflexes [21–24].

14.6 Drug Therapy in the Elderly

Prevalence of prescription drug use among older adults increases substantially with age. Among people ≥ 65 , 90% use at least 1 drug per week, > 40% use at least five different drugs per week and 12% use ≥ 10 different drugs per week. Women take more drugs, particularly psychoactive and arthritis drugs. Drug use is greatest among the frail elderly, hospitalised patients and nursing home residents; typically, a nursing home resident is given 7–8 different drugs on a regular basis [25].

Providing safe, effective drug therapy for the elderly is challenging for many reasons:

- They use more drugs than any other age group, increasing risk of adverse effects and drug interactions, and making adherence more difficult.
- They are more likely to have chronic disorders that may be worsened by the drug or affect drug response.
- Their physiologic reserves are generally reduced and can be further reduced by acute and chronic disorders.
- Ageing can alter pharmacodynamics) and pharmacokinetics.
- They may be less able to obtain or afford drugs.

There are two main approaches to optimising drug therapy in the elderly:

- Using appropriate drugs as indicated to maximise cost-effectiveness
- Avoiding adverse drug effects

Because the risk of adverse drug effects is higher, overprescribing (polypharmacy) has been targeted as a major problem for the elderly. However, underprescribing appropriate drugs must also be avoided.

14.7 Drug-Related Problems in the Elderly

Drug-related problems are common in the elderly and include drug ineffectiveness, adverse drug effects, overdose, underdose and drug interactions.

14.7.1 Before Starting a New Drug

To reduce the risk of adverse drug effects in the elderly, clinicians should do the following before starting a new drug:

- Consider nondrug treatment
- Discuss goals of care with the patient
- Document the indication for each new drug (to avoid using unnecessary drugs)
- Consider age-related changes in pharmacokinetics or pharmacodynamics and their effect on dosing requirements
- Choose the safest possible alternative (e.g. for non-inflammatory arthritis, acetaminophen instead of an NSAID)
- Check for potential drug–disease and drug–drug interactions
- Start with a low dose
- Use the fewest drugs necessary
- Note coexisting disorders and their likelihood of contributing to adverse drug effects
- Explain the uses and adverse effects of each drug
- Provide clear instructions to patients about how to take their drugs (including generic and brand names, spelling of each drug name, indication for each drug and explanation of formulations that contain more than one drug) and for how long the drug will likely be necessary
- Anticipate confusion due to sound-alike drug names and pointing out any names that could be confused (e.g. Glucophage[®] and Glucovance[®])

14.7.2 After Starting a Drug

The following should be done after starting a drug:

- Assume a new symptom may be drug related until proved otherwise (to prevent a prescribing cascade).
- Monitor patients for signs of adverse drug effects, including measuring drug levels and doing other laboratory tests as necessary.
- Document the response to therapy and increase doses as necessary to achieve the desired effect.
- Regularly re-evaluate the need to continue drug therapy and stop drugs that are no longer necessary.

14.7.3 Ongoing

The following should be ongoing:

- **Medication reconciliation** is a process that helps ensure transfer of information about drug regimens at any transition point in the healthcare system. The process includes identifying and listing all drugs patients are taking (name, dose, frequency, route) and comparing the resulting list with the physician's orders at a transition point. Medication reconciliation should occur at each move (admission, transfer and discharge).

- **Computerised physician ordering programs** can alert clinicians to potential problems (e.g. allergy, need for reduced dosage in patients with impaired renal function, drug–drug interactions). These programs can also cue clinicians to monitor certain patients closely for adverse drug effects.

14.7.4 Cardiac Effect of Anticancer Therapy in the Elderly

The elderly are historically underrepresented in clinical trials, with patients older than age 65 years representing only 38% of enrolled patients. For this reason, less is known about long-term risks in this population of cancer survivors.

Cancer treatments, including chemotherapy, targeted therapy and hormonal therapy, have multiple short- and long-term toxicities, but one of the most concerning is cardiac toxicity. Anticancer therapies can also have indirect effects, such as alterations in blood pressure, or can cause metabolic abnormalities that subsequently increase risk for cardiac events [6, 18, 26–28].

14.7.5 Anthracycline

Anthracyclines are part of most chemotherapeutic regimens for the treatment of many malignancies encountered in the elderly. Toxicity that is observed more frequently is a form of cardiomyopathy that manifests itself during the therapy with doxorubicin in the greatest part of the cases, 86, and it has been reported that the incidence of congestive heart failure following treatment with anthracyclines increases progressively with age after 70 years; these results are confirmed by a multivariate analysis [29].

This may explain why many elderly patients are either excluded from anthracycline treatment or receive less-aggressive chemotherapy.

However, anthracyclines remain the cornerstone of first-line therapy for non-Hodgkin's lymphoma (NHL) and metastatic cancers, and the decision to treat involves balancing likely benefit against possible risks [30, 31].

Anthracycline administration techniques and modality may also affect cardiac risk in the elderly:

Duration and Frequency of Administration

- A Cochrane review of five randomised controlled trials predominantly involving adult patients concluded that continuous infusion of 6 h or longer significantly reduced the risk of clinical heart failure (and probably also subclinical cardiac damage) when compared with infusions of 1 h or less [relative risk (RR) 0.27; 95% confidence interval (CI) 0.09–0.81] [32].
- In the early retrospective study of Von Hoff et al. [33], weekly administration was associated with less CHF than a 3-week schedule.

Type of Anthracycline

- **Epirubicin** is less cardiotoxic than **doxorubicin** and the Cochrane Review of the evidence from controlled trials has recently confirmed a lower rate of CHF with no difference in response rate and survival observed in patients treated with epirubicin compared with doxorubicin [34].

■ **Table 14.2** Preventable causes of drug-related problems

Category	Definition
Drug interactions	Use of a drug results in a drug–drug, drug–food, drug–supplement or drug–disease interaction, leading to adverse effects or decreased efficacy
Inadequate monitoring	A medical problem is being treated with the correct drug, but the patient is not adequately monitored for complications, effectiveness or both
Inappropriate drug selection	A medical problem that requires drug therapy is being treated with a less-than-optimal drug
Inappropriate treatment	A patient is taking a drug for no medically valid reason
Lack of patient adherence	The correct drug for a medical problem is prescribed, but the patient is not taking it
Overdosage	A medical problem is being treated with too much of the correct drug
Poor communication	Drugs are inappropriately continued or stopped when care is transitioned between providers and/or facilities
Underprescribing	A medical problem is being treated with too little of the correct drug
Untreated medical problem	A medical problem requires drug therapy, but no drug is being used to treat that problem

- **Pegylated liposomal doxorubicin** has shown similar efficacy and improved cardiac safety compared with that of conventional doxorubicin (HR = 3.16, 95% CI 1.58–6.31, $P < 0.001$) [35, 36] (■ Table 14.2).

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