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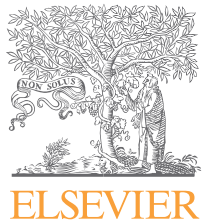

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SIOG (International Society of Geriatric Oncology) and anthracycline use in the elderly

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ABSTRACT

The management of cancer in elderly patients is a complex area that requires specialist expertise. Historically, elderly patients have been under-represented in clinical trials, though this situation is improving, and hence there is a lack of evidence on which to base authoritative guidelines. A comprehensive geriatric assessment can be useful in assessing the patient's overall health status and life expectancy, and hence in guiding treatment decisions. Elderly patients who are fit, or who have medical problems that are amenable to treatment, should receive the same care as younger patients, whereas unfit or frail patients may require interventions tailored to geriatric patients, such as non-aggressive treatment and palliative therapy. There is evidence that adjuvant chemotherapy is beneficial in elderly patients with breast cancer, and that age *per se* should not be a contraindication to such treatment in an otherwise healthy elderly patient. However, anthracycline-related cardiotoxicity is a particular concern in elderly patients because this group is more susceptible to the cardiotoxic effects of anthracyclines than younger patients, and hence heart failure may develop at lower cumulative doses. A recent expert opinion on anthracycline use in elderly patients, published by the International Society of Geriatric Oncology (SIOG), recommends screening to identify patients at high risk of cardiotoxicity, the use of agents with a low cardiotoxicity risk, such as liposomal doxorubicin formulations, and regular monitoring of cardiac function during treatment.

1. Introduction

Many solid tumours and haematological malignancies are more common in elderly than in younger patients. For example, approximately two-thirds of colorectal cancer cases [1] and half of all new breast cancer cases [2] occur in patients over 65 years of age. Thus, the incidence of these cancers is likely to grow as populations age both in Western countries and in large developing countries such as India and China, creating an increasing need to treat elderly cancer patients. However, the treatment of this population is problematical: patients vary considerably in their fitness levels, and also generally have a higher cardiac risk than younger patients, thereby increasing their susceptibility to cardiotoxicity following treatments such as anthracyclines or trastuzumab. Specialist expertise is therefore necessary to manage elderly patients with cancer.

Interest in the treatment of cancer in the elderly is a relatively recent specialism, [3] which can be dated back to 1983 when the National Cancer Institute and the National Institute on Aging convened a landmark meeting, *Perspectives on the Prevention and Treatment of Cancer in*

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the Elderly. Subsequent milestones in the development of the specialty included the Venice Statement on the treatment of cancer in the elderly,[4] and the formation of the International Society of Geriatric Oncology (SIOG) in 2000. SIOG has published guidelines for comprehensive geriatric assessments,[5] which now form a keystone of cancer management in elderly patients. More recently the same organisation has developed a position paper on the management of anthracycline-related cardiotoxicity in elderly patients with cancer.[6] This paper reviews a number of key issues in the treatment of cancer in elderly patients, and summarises the SIOG recommendations for anthracycline use in the elderly.

2. The evidence base for cancer treatment in elderly patients

Historically, elderly patients have been under-represented in clinical trials, despite the high incidence of cancers in this population. For example, in 164 Southwestern Oncology Group (SWOG) trials between 1993 and 1996, only 22% of patients were at least 65 years old, and only 8–13% of patients were aged 70 years or more; this under-representation was particularly noticeable in some conditions that disproportionately affect the elderly, such as lymphoma.[1,7] The situation has changed somewhat in the last decade, and more randomised clinical trials are being conducted specifically in elderly patients,[8] facilitating the development of evidence-based guidelines.[3]

3. Definition and assessment of elderly patients

'Elderly' patients are often defined as those over 65 years of age, but in practice they are a highly heterogeneous population:[1] patients of the same chronological age have different levels of fitness, comorbidities and life expectancy. This heterogeneity will affect treatment decisions, particularly relating to toxic therapies. Hence, a comprehensive geriatric assessment (CGA), which evaluates patients on several domains of ageing (cognition, comorbidities, emotional conditions, function, geriatric syndromes, nutrition, pharmacy and socioeconomic conditions) can be helpful in determining the most appropriate treatment.[9] The CGA is a well-established tool for assessing the health status and risks of morbidity, mortality and toxicity in elderly patients.[5] However, it is currently unclear whether this assessment helps to identify patients who would benefit from chemotherapy with anthracyclines. Nevertheless, if an elderly patient is not fully assessed, some issues may be missed that could affect their outcomes over the next few years. Moreover, there is evidence that interventions dictated by proper assessment of elderly patients can have a comparable impact on long-term outcome to adjuvant therapy in breast cancer or the use of beta-blockers following myocardial infarction in the general population.[10–12]

3.1. *Health status as a guide to treatment in the elderly*

The concept of health status groups may be useful in predicting patients' life expectancy, and hence in making treatment decisions. Elderly patients may be divided into three cohorts according to their health status (fit, median life expectancy, and frail). In patients at all ages, the fittest have a longer life expectancy than the frailest; for example, among patients who are 80 years old, the fittest have a median life expectancy of 13 years for women and 10.8 years for men, compared with 4.6 and 3.3 years, respectively, in frail patients (Fig. 1).[13]

As noted above, elderly patients have traditionally been under-represented in clinical trials, and hence treatment decisions must be based on a general assessment of their health status and 'fitness'. However, it is often difficult to judge which category a patient will fall into, and hence the most appropriate treatment for that patient, although some general guidelines can be proposed. Elderly patients who are fit, or those who have some problems that can be ameliorated by an intervention, should receive standard treatment as in younger patients. Those who have a worse health status and multiple problems that cannot be easily improved should receive interventions tailored to geriatric patients, such as non-aggressive treatment and palliative treatment: adjuvant therapy may not be appropriate for many of these patients.

4. Factors limiting chemotherapy in elderly breast cancer patients

There are some limitations to the use of cytotoxic chemotherapy in the elderly. A key factor is renal function, as many of the drugs are excreted by the kidneys and so may produce considerable toxicity in elderly patients with renal impairment. Other issues include liver function, drug distribution and absorption, bone marrow reserves and neurological factors.[1] These limitations also apply to younger patients, but are more acute in the elderly. Furthermore, elderly patients often have comorbidities that require medication, and so drug interactions may further complicate chemotherapy in this population.

Despite these limitations, there is evidence that adjuvant chemotherapy is beneficial in some elderly patients with breast cancer. For example, in the recent CALGB 49907 trial, standard therapy with either doxorubicin plus cyclophosphamide or cyclophosphamide–methotrexate–fluorouracil (CMF) was found to be superior to capecitabine in women with early breast cancer aged 65 years and older.[14] After a median follow-up of 2.4 years, the hazard ratio (HR) for recurrence in

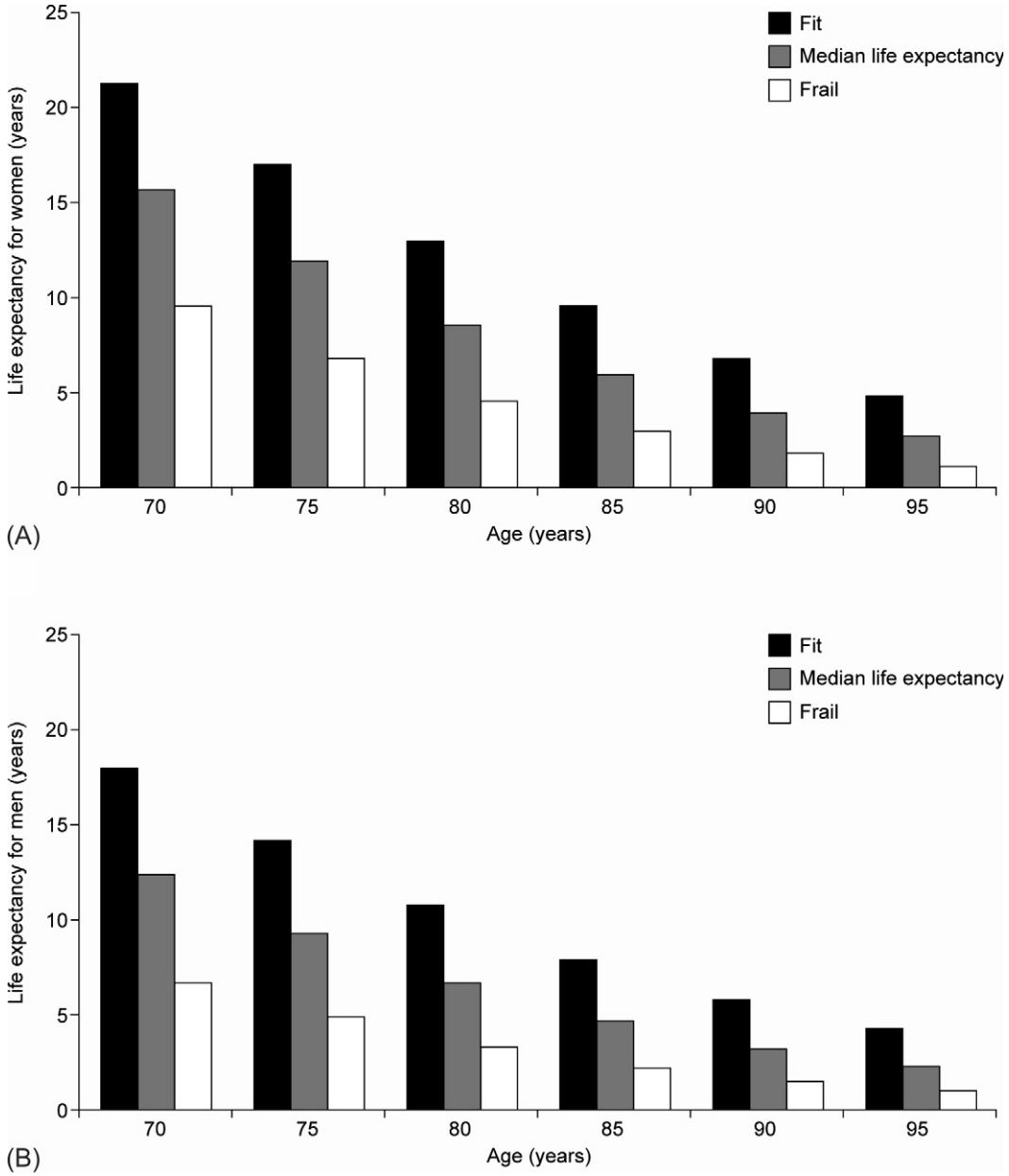

Fig. 1 – Median life expectancy in elderly patients of different ages, according to health status (fit, median life expectancy, frail). [13] **(A) Life expectancy for women; (B) life expectancy for men. Reprinted with permission from Walter LC, Covinsky KE. Cancer screening in elderly patients: a framework for individualized decision making. *JAMA* 2001;285:2750–6. Copyright ©2001 American Medical Association. All rights reserved.**

patients receiving capecitabine was 2.09 (95% confidence interval [CI] 1.38–3.17, $P < 0.001$), compared with those receiving standard therapy. At 3 years, relapse-free and overall survival rates were 85% and 91%, respectively, with standard chemotherapy and 68% and 86%, respectively, with capecitabine. Furthermore, in a meta-analysis of 46 trials involving approximately 6000 women with early-stage oestrogen receptor-poor breast cancer, patients who received non-taxane-based chemotherapy, irrespective of age, had longer disease-free and overall survival than those who did not. [11] Such findings suggest that age *per se* should not be considered a contraindication to adjuvant chemotherapy in otherwise healthy breast cancer patients. [15]

5. Anthracycline-related cardiotoxicity

Cardiotoxicity, characterised by irreversible cumulative myocyte damage caused by oxidative stress, is a known complication of anthracycline use that can lead to dilated cardiomyopathy and hence to systolic dysfunction and congestive heart failure (CHF). [16] The incidence of

CHF increases from >4% at a doxorubicin cumulative dose of 500–550 mg/m^2 to approximately 36% at a cumulative dose of at least 600 mg/m^2. [16] Anthracycline-related cardiotoxicity may be difficult to recognise in elderly patients, who often have non-treatment-related symptoms that may mask or mimic the symptoms of CHF. [17] In addition, patients may not report new symptoms to their clinicians, because they attribute them either to their chemotherapy or their underlying disease. For these reasons, clinical judgement may not be sufficient to assess whether a patient already has background cardiac problems, and hence whether they are suitable for anthracycline therapy.

Potential markers of cardiac damage in anthracycline-treated patients include troponin I [18] and brain natriuretic peptide. [19] An approach that is often suggested is to monitor left ventricular ejection fraction during treatment, by means of echocardiography or multi-gated acquisition scans. [20] However, such measurements are relatively insensitive, and are subject to considerable inter-operator variation. Moreover, they detect cardiotoxicity only once it has become manifest as left ventricular dysfunction, whereas blood tests may detect cardiotoxicity at an earlier stage. Potential strategies for reducing anthracycline-related cardiotoxicity include the use of liposomal doxorubicin formulations, which have been shown to provide comparable efficacy to conventional doxorubicin, with a lower incidence of cardiotoxicity, in patients with metastatic breast cancer. [21–24]

5.1. *Cardiotoxicity in elderly patients*

Anthracycline-related cardiotoxicity represents an important clinical problem in elderly cancer patients. In one study, breast cancer patients aged 66–70 years who had received adjuvant anthracyclines showed a significantly higher incidence of CHF (adjusted HR 1.26, 95% CI 1.12–1.42) than those who had received no chemotherapy or non-anthracycline regimens, and this difference continued to increase with longer follow-up. [25] Furthermore, anthracycline-related cardiomyopathy has a worse outcome than idiopathic cardiomyopathy. [26] The issue is a particular concern in elderly patients because this age group is more susceptible than younger patients to the cardiotoxic effects of anthracyclines, and so heart failure develops at lower cumulative doses. [27]

The problem of anthracycline-related cardiotoxicity has been exacerbated since the introduction of trastuzumab because, although the addition of this agent to anthracycline-based and taxane-based regimens markedly improves survival, it is associated with an increased risk of cardiac adverse events. [28] However, a recent phase I/II study in patients with metastatic breast cancer has shown that combination therapy with non-pegylated liposomal doxorubicin, paclitaxel and trastuzumab produces good efficacy with acceptable levels of cardiac and general toxicity: the overall response rate was 98%, and there were no cases of clinical CHF. [29]

6. SIOG expert opinion on anthracycline treatment in elderly patients

The SIOG expert opinion on anthracycline use in elderly patients (Fig. 2) recommends rigorous screening to exclude patients with an unacceptable level of cardiovascular risk, and careful attention to dosing

Rigorous screening to exclude patients at unacceptably high cardiac risk (Level 1a)
- comprehensive patient history
- current signs or history of CHF
- cardiovascular comorbidity (i.e. hypertension, diabetes or coronary artery disease)
- prior exposure to anthracyclines for this or previous malignancy (all 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; Level 5 in elderly)
- liposomal anthracycline formulations (Level 1b; Level 5 in elderly)
- sequential administration of conventional anthracyclines and trastuzumab in HER2-positive breast cancer (Level 1b; Level 5 in elderly)

Regular monitoring of cardiac function, signs and symptoms (Level 1a)
- measurement of LVEF by ultrasound (preferred, Level 5) or MUGA scan[a] every 2–3 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)

Fig. 2 – International Society of Geriatric Oncology (SIOG) recommendations for the use of anthracyclines in elderly patients. [6] Level 1a evidence: systematic review of randomised clinical trials; Level 1b evidence: individual randomised clinical trial; Level 5 evidence: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'. [a]Use the same method through follow-up. ACE, angiotensin-converting enzyme; CHF, congestive heart failure; HER2, human epidermal growth factor receptor-2; LVEF, left ventricular ejection fraction; MUGA, multi-gated acquisition scan. Reprinted from Aapro M, et al. Anthracycline cardiotoxicity in the elderly cancer patient: a SIOG expert position paper. *Ann Oncol* 2011;22(2):257–67, with permission from Oxford University Press.

to ensure that maximum cumulative doses are not exceeded.[6] In addition, the authors advocate the use of less cardiotoxic therapy, such as liposomal doxorubicin formulations, with regular monitoring of cardiac function and appropriate cardiovascular risk reduction measures. In general, these recommendations are supported by a strong evidence base (Level 1a – systematic review of randomised clinical trials, or Level 1b – individual randomised clinical trial), although it should be noted that due to the lack of clinical trials in elderly patients the evidence in some cases is less strong in the elderly (Level 5 – expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles').

7. Conclusions

The treatment of elderly patients with cancer is a complex area. There is currently insufficient evidence to formulate evidence-based recommendations in geriatric oncology, although this situation is improving, and the impact of old age on treatment-related cardiac problems is poorly understood. It is important to refine treatment algorithms for older patients, to ensure they receive optimal therapy. In addition, practical assessment tools are needed to evaluate the patient's status and guide decisions about the best use of effective treatments such as anthracyclines. The patient's best interests, particularly in terms of their long-term life expectancy, should always be paramount.

8. Conflict of interest statement

Dr Aapro has received honoraria from Cephalon.

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