Anthracycline cardiotoxicity in the elderly cancer patient: a SIOG expert position paper


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Background: Comorbidities and risk factors likely to complicate treatment are common in elderly cancer patients. Anthracyclines remain the cornerstone of first-line therapy for non-Hodgkin’s lymphoma (NHL) and metastatic and early breast cancer but can cause congestive heart failure. Elderly patients are at increased risk of this event and measures to reduce it should be considered.

Methods: A committee of experts in breast cancer and NHL met under the auspices of the International Society for Geriatric Oncology to review the literature and make recommendations, based on level of evidence, for the assessment, treatment and monitoring of elderly patients requiring anthracyclines.

Results and recommendations: Use of anthracycline-based chemotherapy illustrates many of the dilemmas facing elderly cancer patients. Age in itself should not prevent access to potentially curative treatment or treatment that prolongs life or improves its quality. The risk of cardiotoxicity with conventional anthracyclines is increased by the following factors: an existing or history of heart failure or cardiac dysfunction; hypertension, diabetes and coronary artery disease; older age (independent of comorbidities and performance status); prior treatment with anthracyclines; higher cumulative dose of anthracyclines and short infusion duration. The fact that cumulative and irreversible cardiotoxicity is likely to be greater in this population than among younger patients calls for effective pretreatment screening for risk factors, rigorous monitoring of cardiac function and early intervention. Use of liposomal anthracycline formulations, prolonging the infusion time for conventional anthracyclines and cardioprotective measures should be considered. However, when treatment is being given with curative intent, care should be taken to ensure reduced cardiotoxicity is not achieved at the expense of efficacy.

Key words: anthracyclines, breast cancer, cardiotoxicity, elderly, liposomal anthracyclines, non-Hodgkin’s lymphoma

introduction

Anthracyclines are among the most effective drugs in both solid and haematological malignancies but have significant side-effects. They are known to cause both short- and long-term cardiotoxicity, including potentially fatal congestive heart failure (CHF) [1]. Elderly patients are likely to be particularly susceptible to these problems because of comorbidities, such as hypertension and diabetes, and limited cardiac reserve [2]. Since the incidence of cancer increases with age and the number of older people is rising, there is a growing population of elderly patients with cancer. By the end of the next decade, it is estimated that in many countries, 70% of all newly diagnosed cancers will be in patients older than 65 years [3]. The appropriateness of standard anthracycline-based chemotherapy in elderly patients is therefore an important issue. This paper concentrates on breast cancer and non-Hodgkin’s lymphoma (NHL) because these tumours account for a large burden of disease among older people [4, 5]. However, the issues raised are applicable to other malignancies in which anthracyclines play a central role in treatment.

chemotherapy in the elderly: general considerations

While chronological ageing is uniform and relentless, biological ageing is not. Many 75-year-old cancer patients are at least as fit
as some patients aged 65 years; and their willingness to accept treatment, which may extend their lives, even though it is associated with significant toxic effects, can be just as great [6]. Although the elderly account for the majority of patients with cancer and receive most of the chemotherapy administered, they are generally under-represented in major clinical trials [7, 8]: only 25% of 16 000 patients enrolled in trials covering 15 different tumour types between 1993 and 1996 [7] were aged 65 years or older and 63% of the general cancer population was at least 65 years. Only 16% of the breast cancer patients enrolled in the recent pivotal trials of adjuvant trastuzumab were aged 60 years or older [9, 10] (although this reflects in part the fact that Human Epidermal growth factor Receptor 2 (HER2) positive disease is more common in younger women than in older women). We therefore have less knowledge about the potential benefits and risks of cytotoxic and associated therapies in the elderly patients than we have in younger patients [8]. The benefit of anticancer treatments in reducing mortality may be lessened by competing causes of death and long-term follow-up data, in particular, are sparse. Particularly in the elderly cancer patient, the potential benefits of treating the tumour must be balanced against the risk of worsening comorbidities; and the point of balance will vary from one cancer site to another. This is well demonstrated in relation to the two types of tumour considered in this paper. Kendal [11] recently assessed the complex interaction between age, comorbidity and cancer site on the chances of death among >780 000 people registered on the Surveillance, Epidemiology and End Results (SEER) database after a cancer diagnosis in the period 1984–1993. The median age at diagnosis was 67 years. Among those with breast cancer who attained an age of 75 years or older during follow-up, the cumulative probability of dying from a comorbid condition far outweighed risk of death from their tumour. For NHL, however, the reverse was true. Even if it is accepted that age per se should not limit access to potentially curative or life-prolonging therapy, elderly cancer patients are more likely than their younger counterparts to have comorbidities that may reduce the tolerability of anticancer treatments and risk factors that may increase the likelihood of adverse events. Thus, data from the SEER-Medicare database show that patients with NHL aged 65 years and older have a high prevalence of diabetes (32%), hypercholesterolaemia (54%) and hypertension (73%) [12]. In a retrospective analysis of 205 patients with NHL aged 80 years or older, Thieblemont et al. [13] found at least one comorbidity in 87% and a history of cardiovascular disease in 50%. Elderly patients are also more likely than younger patients to be taking drugs that have pharmacokinetic interactions with anticancer agents and/or the potential to exacerbate toxicity [14]. All these facts work towards under-treatment in clinical practice [15], partly due to clinicians’ reluctance more than to patients’ unwillingness to be treated. The recent EUROCaRE study compared survival in cohorts of cancer patients who were middle aged (55–69 years) or elderly (70–84 years) when diagnosed during the period 1988–2002 [16]. In the period analysis of the most recent data, relative survival was far higher in middle-aged patients than in the elderly.

These suggestions of under-treatment of the elderly should not blind us to the fact that over-treatment is also a potential problem. This may result from extrapolating the results of trials in relatively young and fit populations to groups, which are older and less fit. Nevertheless, intensive cancer therapy in fit elderly patients even with moderately chemoresistant tumours can benefit survival to the same extent as in younger patients. This has been demonstrated, e.g. in the case of combined chemoradiotherapy for stage III non-small-cell lung cancer [17]. However, haematological and other toxic effects are likely to be encountered with increased frequency even when the elderly patients concerned have good performance status [18]. Such considerations have led SIOG [International Society of Geriatric Oncology (Société Internationale d’Oncologie Gériatrique)] and others to call for randomised controlled trials to be conducted specifically in elderly patients and for data from existing trials to be reanalysed by age. To give objective information, each statement is assigned a level of evidence according to the system used by the Oxford Centre for Evidence-based Medicine [19] (see ‘Conclusions’ section and ‘Recommendations’ section and Table 3).

**anthracycline-induced cardiotoxicity**

Any decision to treat involves balancing likely benefit against possible risks. Anthracycline cardiotoxicity has been a concern for almost as long as this important and effective class of drugs has been used [20, 21].

**characteristics**

Rarely, doxorubicin causes acute cardiac toxic effects during or soon after administration: ECG changes, arrhythmias and pericarditis–myocarditis syndromes have been reported [2, 22, 23]. These events generally resolve and do not necessarily relate to the more clinically significant long-term risk of CHF, which can seriously impair quality of life and on occasions prove fatal. The longer term cardiotoxicity of anthracyclines has been highlighted in paediatric patients: in one series, follow-up of 10–20 years showed a 23% incidence of late cardiac abnormalities [24]. However, the risk exists in all cancer populations [1, 25, 26]. A classic review has shown that a dilated cardiomyopathy characterised by systolic dysfunction and left-sided CHF may occur 2–5 years after treatment [27]. If this happens, outcome is poor: median survival of 1 year is reported in a large population-based series [28].

In the seminal study of anthracycline, Von Hoff et al. [21] found an overall 2.2% incidence of drug-induced CHF among 4 018 patients treated with doxorubicin. Risk was consistently related to dose administered and to advancing age (Table 1). This was one of the first and largest studies to document risk factors for cardiotoxicity with anthracyclines demonstrating a cumulative dose to clinical cardiotoxicity of doxorubicin. If the overall incidence of CHF in this study was relatively low, this may relate to the limitations of retrospective analysis (incomplete reporting, lack of prospective serial cardiovascular assessment and a lower than planned administration of drug) [21].

Data from three trials (two in breast and one in non-small-cell lung cancer) conducted between 1988 and 1992 in which cardiotoxicity was prospectively assessed showed that the rate of conventional doxorubicin-related CHF was 5% at
Table 1. Doxorubicin-induced cardiotoxicity is related with cumulative dose [21]

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<th>Cumulative dose (mg/m²)</th>
<th>Probability of heart failure (%)</th>
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<td>40–59 years old</td>
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<td>250</td>
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A cumulative dose of 400 mg/m², 16% at a dose of 500 mg/m² and 26% at a dose of 550 mg/m² [26]. Age was clearly a risk factor, with a hazard ratio (HR) of 2.25 in patients older than 65 years compared with those aged 65 years or younger. Adjustment of the proportional hazards model for covariates including history of cardiovascular disease, left ventricular ejection fraction (LVEF) approaching the lower limit of normal and Eastern Cooperative Oncology Group performance status reduced the HR only slightly, to 2.12. Age was therefore essentially an independent risk factor among these patients selected as fit for trial entry.

CHF following anthracyclines appears to be caused by cumulative damage to myocytes [1]. This form of toxicity may appear at doses lower than those responsible for acute cardiac events, is dose related (and hence predictable) and irreversible. However, individual susceptibility to cardiomyopathy is highly unpredictable. In addition to clinical CHF, anthracycline-based chemotherapy is associated with an insidious subclinical cardiomyopathy [26]. Twenty-five percent of women who received six cycles of cyclophosphamide, epirubicin and 5-fluorouracil developed an asymptomatic decline of 10% or more in LVEF after 5 years [29]. Other factors that stress the heart, such as hypertension and developing coronary disease, can add progressively to the subclinical damage already caused by anthracyclines [1].

The limit of 450 mg/m² for conventional doxorubicin is now quoted as standard for maximum cumulative dose even if this is not a precise cut-off point [2].

**assessment**

Cardiac function during and after anthracycline therapy is generally assessed in terms of LVEF, determined either by echocardiography or by multiple uptake gated acquisition scintigraphy [30]. Magnetic resonance imaging is not suggested as it is not widely available. However, LVEF is an imperfect guide to cardiotoxicity, not able to detect subtle changes in myocardial function [30, 31]. The heart’s ability to compensate is so great that severe damage can be sustained before this is evident in measurable reductions in LVEF. However, once the ability to compensate is exceeded, decline into heart failure can be rapid. A related point is that heart failure can occur in the absence of reduced LVEF [1]. Indeed, impaired diastolic function is emerging as an early sign of cardiotoxicity [32].

Serum biomarkers such as N-terminal-pro-brain natriuretic peptide (NT-proBNP), cardiac troponin or creatinine kinase MB have been assessed as a possible means of early detection of cardiac dysfunction induced by anthracyclines. However, results to date are not consistent: certain studies suggest a role for these markers, particularly NT-proBNP [33], while others failed to find any advantage over the monitoring of LVEF [34].

is there less cardiotoxic anthracycline alternative to doxorubicin?

**duration and frequency of administration.** The extent to which anthracycline efficacy depends on peak concentration is still uncertain. Toxicity is thought to be a function of both peak concentration and total exposure. Whether peak concentration is elevated in the elderly is debated [35, 36]. If so, this would be additional reason for caution in older patients and for considering the option of prolonged infusion. 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] [37]. There was no evidence that continuous infusion reduced response rate or survival. Continuous infusion would therefore appear to be clearly less cardiotoxic, although this form of administration may in some circumstances be impractical.

In the early retrospective study of Von Hoff et al. [21], weekly administration was associated with less CHF than a 3-week schedule. But frequent hospital visits may be a disadvantage for certain elderly patients, particularly those with limited mobility; and there is a question mark over equivalent efficacy.

It has been suggested for a long time that 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 [38]. Maximum cumulative dose of 900 mg/m² is considered as the standard [2].

Long-term data from the French Adjuvant Study Group confirm that age older than 65 years was also a risk factor for epirubicin cardiotoxicity, even though the incidence of left ventricular dysfunction (1.36% at 10 years) was considered low [39].

**liposomal formulation.** Liposomal anthracyclines were designed with the intent to reduce the risk of cardiotoxicity related to conventional doxorubicin while preserving antitumour efficacy. Encapsulation of anthracyclines in liposome modifies the pharmacokinetics of the drug leading to selective uptake by and reduced clearance from tumour as opposed to healthy tissues [40, 41]. Uncoated liposomal doxorubicin was associated with a lower risk of cardiac events than conventional doxorubicin (significantly reduced risk of the end point of combined clinical and subclinical heart failure: RR 0.38, 95% CI 0.24–0.59), with no difference in response rate and survival [38]. In a large, phase III randomised study conducted in first-line metastatic breast cancer, 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, \( P < 0.0001 \)) [42].

dexrazoxane. The use of this iron-chelating agent, which scavenges free radicals, has been recommended by the American Society of Clinical Oncology for anthracycline-pretreated metastatic patients as a possible means of reducing cardiotoxicity (cumulative doxorubicin dose >300 mg/m²). Unfortunately, there are no studies in the elderly setting [43, 44].

other measures. Certain authors recommend other potentially protective measures in high-risk patients needing anthracyclines. Single-centre studies have suggested that use of beta blockers [45] and angiotensin-converting enzyme inhibitors [46] in combination with anthracyclines may prevent the development of later cardiotoxicity. However, the studies involved small numbers of patients with limited long-term follow-up. Of note, these drugs are not preventing myocyte damage but only improving the heart’s compensatory mechanisms [2].

breast cancer

In Europe in 2006, 13.5% of cancer cases diagnosed (excluding nonmelanoma skin cancers) are breast cancers [47]. The median age at diagnosis in developed countries is 61 years: more than 40% of cases occur in women aged 65 years or older and more than 20% of cases are in women older than 75 years [4]. If the elderly population expands at projected rates, the prevalence of breast cancer in older women will increase by a third over the next 10 years.

adjuvant therapy

evidence of benefit. The steady reduction in age-standardised breast cancer mortality seen over the past two decades has been attributed not only to improved screening but also to the efficacy of adjuvant therapy in reducing risk of recurrence (http://info.cancerresearchuk.org/cancerstats/types/breast/mortality) [48, 49]. Substantial benefits from adjuvant therapy have been showed in postmenopausal women in all age groups [50] and the gain in patients older than 70 years was in the same range as that in women aged between 50 and 70 years, even if not significant due to the small numbers. Importantly, use of cytotoxic agents is beneficial in many women, especially those with poorer prognosis disease [51], or when the disease becomes endocrine resistant: adjuvant chemotherapy was associated with a 15% relative reduction in mortality among women aged 66 years and older with hormone-receptor-negative breast cancer (adjusted HR 0.85, 95% CI 0.77–0.95) [52]. The benefit of chemotherapy was higher in women with involved lymph nodes (24% reduction in risk of death) than in those who were node negative.

The risk of recurrence and the period over which this risk applies vary with the pathological features of the primary tumour. Thus, hormone-receptor-negative, HER2-positive high-grade tumours carry a large risk of early recurrence while estrogen-receptor-positive low-grade tumours recur at a lower rate but over a longer period [53]. For a woman to experience benefit from adjuvant therapy, her non-breast cancer-related life expectancy must be sufficiently long for the threat of recurrence to be appreciable, and the advantages of preventing a recurrence must outweigh the potential toxicity of treatment. In the United States, women life expectancy falls below 5 years only when they reach the age of 90 years, but an average 65-year-old woman can expect to live a further 20 years, an average 75-year-old a further 12 years, and an average 80-year-old a further 9 years [54]. Importantly, according to studies, among women for whom adjuvant chemotherapy is indicated, the majority of relapses occur within the first 2–3 years [55].

Anthracycline-containing combination chemotherapy reduces cumulative 10-year breast cancer mortality by an absolute 4.6% when compared with non-anthracycline-based regimens [48]. The French Adjuvant Study Group randomised women older than 65 years with node-positive disease to either tamoxifen alone or tamoxifen plus six cycles of weekly epirubicin 30 mg [56]. Despite the lack of impact on overall survival, use of the anthracycline was associated with a reduced risk of relapse at 6 years (on multivariate analysis), with a 2% rate of reduced LVEF following adjuvant chemotherapy. A more recent study demonstrated that capecitabine, considered as a less aggressive regimen, leads to almost twice the rate of disease recurrence and death when compared with standard chemotherapy either CMF (cyclophosphamide, methotrexate and fluorouracil) or cyclophosphamide plus doxorubicin in women aged 65 years and older with early breast cancer [57].

Adjuvant therapy with docetaxel (Taxotere®, Sanofi Aventis, France) plus cyclophosphamide (TC) should be an alternative to doxorubicin plus cyclophosphamide (AC) in patients at higher cardiac risk. This regimen is associated with significantly longer disease-free and overall survival [58]. Sixteen percent of patients in this trial were older than 65 years and TC was superior to AC in this group, as it was in younger patients. However, the highest level of evidence requires a confirmatory study.

incidence of cardiotoxicity. Prospective data on the long-term adverse consequences of adjuvant therapy in elderly patients with breast cancer are sparse. However, a retrospective study of patients with early breast cancer treated with doxorubicin within four prospective trials conducted at the M.D. Anderson Cancer Center allows the comparison between 65 patients aged 65 years and older with 325 younger patients (aged 50–64 years old) [59]. With a median follow-up of 14 years, cardiopulmonary complications were the cause of death mainly in elderly patients (13% versus 7%). Furthermore, a retrospective analysis using the SEER database to estimate the cumulative rates of CHF among more than 40 000 women aged 66–80 years with no history of heart failure who were diagnosed as having early breast cancer between 1992 and 2002 [60].

Among women aged 66–70 years, the HR for CHF among the 11% of the study population who were treated with adjuvant anthracyclines (compared with those treated with other chemotherapy) was 1.26 (95% CI 1.12–1.42). Within 10 years, 38% of anthracycline-treated women had been diagnosed as having CHF. This compared with 33% of those treated with non-anthracycline chemotherapy and 29% among those who had had no adjuvant chemotherapy. The high rate seen even in
women not receiving cytotoxics demonstrates the cardiac fragility of this age group.

The treatment-related differences emerged despite the fact that women given anthracyclines were on average younger and had fewer comorbid conditions than those not receiving such treatment. In the population studied, age and comorbidities (hypertension, diabetes and coronary artery disease) were significantly predictive of CHF while left-sided chest irradiation was not, likely due to less common conservative approach in the United States than in Europe. Anthracycline chemotherapy was not associated with increased risk in women aged 71–80 years, probably because patients in this older group were particularly carefully selected for absence of cardiovascular risk factors. However, potentially confounding factors aside, this finding suggests that it may be premature simply to advocate non-anthracycline adjuvant regimes for elderly patients as a matter of course. The incorporation of novel targeted agents into anthracycline-based adjuvant chemotherapy is at an early stage, with trastuzumab the only agent approved to date in this setting. The additive cardiotoxicity of trastuzumab and conventionally formulated doxorubicin gave considerable cause for concern. For HER2-positive breast cancer, adding trastuzumab to adjuvant chemotherapy regimens significantly decreases risk of disease recurrence and death [61, 62]. However, risk of heart failure in some settings may be fivefold or greater when trastuzumab is given in conjunction with conventional anthracyclines [63]. While anthracycline cardiotoxicity appears due to oxidative stress on the myocardium, that associated with trastuzumab seems to arise from inhibition of a HER2-mediated cardioprotective mechanism. Given the small number of elderly patients included in clinical trials of anti-HER2 agents [9, 10], the implications of such cardiotoxicity for older women with comorbidities is unclear [64]. Pinder et al. [60] noted in their retrospective analysis of SEER-Medicare data that trastuzumab treatment was a risk factor for development of CHF by elderly breast cancer patients. It is possible that the frequency and severity of such adverse events could be diminished by allowing a period of recovery from doxorubicin before trastuzumab is administered or by the use of a less cardiotoxic form of anthracycline or less cardiotoxic inhibitor of HER2. Preliminary evidence suggests that lapatinib, e.g. may be less cardiotoxic [65, 66].

**metastatic disease**

Although the prospect in metastatic disease is not one of cure, chemotherapy, and in particular anthracycline, has achieved much through palliation of symptoms and extending life, especially in patients with hormone-receptor-negative or endocrine non-responsive disease. However, cardiotoxicity remains an issue in this palliative setting [2], although the focus shifts from avoiding long-term sequelae to more immediate problems that might compromise survival or quality of life. Moreover, the addition of novel targeted agents, such as bevacizumab, to chemotherapy regimen, there is a risk of additive toxic effects. Bevacizumab in combination with chemotherapy has shown increased efficacy first line in metastatic breast cancer [67, 68], but CHF, thromboembolism and hypertension are among its potential toxic effects [69]. The value of this association has been recently questioned by the Food and Drugs Administration Oncologic Drugs Advisory Committee (http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterial/Drugs/OncologicDrugsAdvisoryCommittee/ucm219977.htm).

A major distinction in the metastatic setting is between patients who have received an anthracycline as part of adjuvant therapy and those who have not. In anthracycline-pretreated patients, it is important to establish whether there were (a-)symptomatic reductions in LVEF (or any other indications of early cardiotoxicity), and how long was the free of disease interval since completion of adjuvant treatment (more or less than 1 year).

**cumulative dose.** As in the adjuvant setting, not exceeding the maximum cumulative dose of anthracyclines is an important consideration. Among more than 1000 metastatic breast cancer patients treated with epirubicin-based chemotherapy, the overall rate of cardiotoxicity [defined as New York Heart Association (NYHA) class II or higher CHF] was 11% [70]. In first line, the risk of cardiotoxicity increased by 40% for each 100 mg/m² increase in cumulative dose and by 30% with each decade of age. So the maximum cumulative dose of epirubicin acceptable from the standpoint of cardiotoxicity (i.e. the dose carrying a 5% risk of developing CHF over a follow-up period of 2.5 years) is probably less than had been assumed. However, the wealth of data in the study demonstrates that the acceptable dose depends on a range of factors, including tumour burden, predisposition to heart disease and treatment history (including mediastinal irradiation, endocrine therapy for metastatic disease and prior treatment with CMF). Since the effect of age is the prime consideration of this paper, it is appropriate to cite two illustrations. For a 40-year-old patient with no predisposition to heart disease and no risk factors related to treatment history (including no prior adjuvant anthracyclines), the cumulative dose of epirubicin acceptable from the point of view of cardiotoxicity was 890 mg/m², i.e., close to the 900 mg/m², which is often cited. However, the acceptable cumulative dose is only 732 mg/m² if the patient is aged 70 years. For a 40-year-old patient with no treatment-related risk factors but a predisposition to heart disease, the acceptable maximum dose is 806 mg/m². However, the acceptable cumulative dose is reduced by 200 mg/m² in a comparable patient aged 70 years. This study took into account risk of death from all other causes, including breast cancer (lower doses of epirubicin being associated with a higher risk of this outcome). We do not have comparable data for doxorubicin, and any extrapolation from the conclusions arrived at with epirubicin should be made only with caution.

**alternative agents and formulations.** In anthracycline-pretreated metastatic disease, a wide range of alternative cytotoxic therapy is available: the taxanes, capecitabine, vinorelbine and gemcitabine can all be used, as single agents or in combination [71]. Weekly epirubicin may be a possibility, although more trials on the feasibility and relative cardiotoxicity of this schedule are required.

Less cardiotoxic formulations of doxorubicin are a valuable option (Table 2). Four phase III studies were conducted in
first-line metastatic breast cancer, comparing respectively uncoated or pegylated liposomal doxorubicin with non-liposomal anthracycline [72], same drugs both in combination with cyclophosphamide [73], uncoated liposomal doxorubicin with epirubicin both in combination with cyclophosphamide [74] and pegylated liposomal doxorubicin with doxorubicin [42]. Liposomal formulations have shown similar efficacy with a least the same cardiotoxicity (comparison with epirubicin) [74] or a reduced cardiotoxicity (comparing with doxorubicin) [42, 72, 73]. Also a randomised phase II study of elderly patients or younger patients but considered as unfit has compared two schedules of pegylated liposomal doxorubicin [75]. Although palmoplantar erythrodysesthesia was more frequent with 4-weekly administration, the authors concluded that 50 mg/m² every 4 weeks was the preferred schedule rather than 60 mg/m² every 6 weeks, in which patients experienced considerably more mucositis). Retrospective analysis of two EORTC studies conducted specifically in elderly patients concluded that the 50 mg/m² schedule had a higher therapeutic index and was preferable in this group of patients [76]. However, except in the two latter studies, elderly patients represented less than one-third of patients enrolled in these trials (Table 2).

### Lymphoma

More than half of all lymphomas occur in patients older than 65 years [5] and diffuse large B cell lymphoma (DLBCL) accounts for more than 60% of these cases [77]. While clinical presentation and prognostic parameters in elderly lymphoma patients are similar to those in younger patients, response rates and survival are less good. This is true even when elderly patients are treated with a standard regimen of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP).

Following evidence from randomised trials that the addition of rituximab to chemotherapy improves survival in both follicular lymphoma and DLBCL, use of the antibody has become standard of care for many groups of lymphoma patients, including the elderly [78]. In a study in patients aged 60 years and older (median age 70 years; 8% older than 80 years), the addition of rituximab to standard CHOP (R-CHOP) reduced the risk of treatment failure and improved survival without appreciably increasing toxicity [79].

Historically, elderly NHL patients have survived less long than younger patients even when deaths unrelated to NHL are excluded. This has been attributed to the use of less aggressive treatments in the elderly and/or their poorer tolerance of standard regimens [12]. However, even in a very elderly group of patients, there are now attempts to adjust the intensity of treatment to the nature of the disease. Thus, in a retrospective series of 205 patients aged 80 years and older, 48% of those with aggressive NHL were treated with an anthracycline-based regimen [13]. Despite the fact that few patients (only 4% of the total) were able to receive six to eight cycles of a standard CHOP or R-CHOP regimen, use of anthracycline-based therapy was associated with a higher rate of complete response than non-anthracycline-containing regimens.

#### Anthracyclines remain the gold standard

In the Nordic Group’s randomised trial, 455 untreated patients with aggressive NHL aged 60–86 years were randomised to...
CHOP or a similar regimen in which the 50 g/m² doxorubicin was replaced by 10 mg/m² mitoxantrone (CNOP) [80]. CHOP was significantly superior to CNOP in time to treatment failure and overall survival. The similar study conducted earlier by Sonneveld et al. [81] had found essentially the same result: randomisation to CNOP resulted in a poorer outcome than with CHOP chemotherapy (at 3 years, 42% of CHOP and 26% of CNOP patients were alive). In a randomised study to test a regimen devised specifically for use in elderly patients (70 years and older) with intermediate- and high-grade NHL, VP-16 plus mitoxantrone and prednimustine achieved significantly poorer progression free and overall survival than CHOP [82]. CHOP therefore is still considered the gold standard of treatment, although bendamustine is challenging it.

However, as in breast cancer, use of anthracyclines in NHL is associated with cardiotoxicity. In a series of 141 adult Hodgkin’s lymphoma and NHL patients treated with a median cumulative doxorubicin dose of 300 mg/m², echocardiography at least 5 years after treatment showed subclinical cardiomyopathy (i.e. decreased left ventricular fractional shortening without CHF) in 28% [83]. Along with male sex, higher dose of doxorubicin, radiotherapy and overweight, older age was a risk factor. More recently, investigators have used the SEER database to assess the incidence of CHF and associated risk factors among more than 9000 patients aged 65 years and older who were diagnosed with DLBCL in the period 1991–2002 [84]. Treatment with doxorubicin (any exposure) was associated with a 29% increase in risk of subsequently developing CHF (HR 1.29, 95% CI 1.02–1.62). This risk was significantly and synergistically exacerbated by hypertension. Other risk factors were number of claims made for doxorubicin reimbursement, increasing age, prior heart disease, comorbidities and diabetes. While 79% of patients not exposed to doxorubicin remained free of CHF at 8 years, this was true of only 74% of doxorubicin-treated patients.

In aggressive NHL, the aim in elderly patients—as in the wider population—is cure. R-CHOP is standard treatment and, since doxorubicin is a central component, it is appropriate to investigate the ways of delivering this drug that minimise toxicity. However, the experience noted above with mitoxantrone makes us aware that the search for decreased toxicity may risk decreased tumour control and shorter survival. Adequate demonstration of the non-inferiority of novel regimens in phase III trials would be mandatory in both fit and less fit patient populations.

There is no standard approach to treating recurrent high-grade NHL in elderly patients. However (given what is known about the importance of cumulative dose), a patient who had already been treated with an anthracycline-containing regimen would be unlikely to tolerate a salvage therapy using one of these agents in a standard formulation. In the absence of phase III data, there is an accumulating body of evidence from uncontrolled studies suggesting that liposomal anthracyclines (for which maximum cumulative doses have not been defined) may have potential in maintaining efficacy while reducing toxicity in patients in whom conventional doxorubicin is likely to be poorly tolerated. These include a study in 21 patients with cardiac comorbidities and/or previous treatment with anthracyclines [85] and a pilot study in 20 patients who were frail and elderly (median age 73 years) [86].

In follicular and other indolent lymphomas, the approach is non-curative. R-CHOP is an effective regimen, but other options are available. These include bendamustine plus rituximab [87], rituximab plus mitoxantrone, chlorambucil and prednisolone (R-MCP) [88] and rituximab plus cyclophosphamide, vincristine and prednisone (R-CVP) [89].

Novel anthracyclines such as amrubicin are in development, and novel formulations of existing agents should be further evaluated as a means of extending the therapeutic options available.

**conclusions**

Use of anthracycline-based chemotherapy illustrates many of the dilemmas facing elderly cancer patients and their careers.

The number of cancer patients who are elderly is increasing rapidly, and there is a pressing need for discussion of issues that may complicate their treatment. Traditionally, pivotal trials have upper age limits for enrolment and/or exclude patients with comorbidities that are frequently found among elderly patients. In many situations, clinicians currently lack a good evidence base on which to make judgements about the balance of benefit and risk in older cancer patients, and data from existing studies should where possible be analysed to clarify the influence of age and comorbidity on outcome.

Age in itself should not prevent access to potentially curative treatment or treatment that prolongs life or improves its quality. Perhaps only 20% of elderly breast cancer patients have disease with the biological characteristics that provide a clear indication for adjuvant chemotherapy, but the absolute number of such patients is large. In this case, for example, patients in their 70s have sufficient life expectancy to benefit from a reduced rate of tumour recurrence. The same is true of potentially curative therapy for aggressive NHL. A corollary of this is that elderly patients’ life expectancy is also sufficient for potential long-term toxic effects to become apparent. Cardiotoxicity risk, increasing dramatically with age contributes towards a reluctance to administer conventional doxorubicin to elderly patients. Alternative in the adjuvant setting are to give epirubicin or a non-anthracycline-based regimen, e.g. TC. Anthracyclines remain the cornerstone of...
first-line therapy for metastatic breast cancer, but liposomal formulations of doxorubicin are a valuable alternative.

The following non-overlapping factors have been identified: an existing or history of heart failure or cardiac dysfunction; comorbidities such as hypertension, diabetes and coronary artery disease (all increasing greatly in frequency with age); older age (a risk factor which is also independent of comorbidities and performance status); prior treatment with anthracyclines and higher cumulative dose of anthracyclines. With the advent of antibody (i.e. trastuzumab and bevacizumab) and small molecular inhibitors of signalling (tyrosine kinase inhibitors) within and around the cancer cell, treatment of the tumour enters a new era of complexity. A corollary is the risk of new and additive toxic effects. Thus, the fact that cumulative and irreversible cardiotoxicity is likely to be greater in this population than among younger patients, calls for effective pretreatment screening for risk factors, rigorous monitoring of cardiac function and early intervention (Table 4).

**SIOG recommendations**

A proportion of elderly cancer patients are clearly frail, and some too sick to countenance cytotoxic chemotherapy. A proportion is clearly fit, and as capable as their younger counterparts of withstanding the toxic effects of treatment. However, the bulk of patients lies somewhere between these extremes. They are reasonably fit, but vulnerable. In such patients, there is a good case for avoiding risk of toxicity whenever that is an option (Table 4).

In the case of aggressive NHL, options for therapy are more limited than in breast cancer, and anthracyclines remain the foundation stone of effective management, although bendamustine is challenging it. Curative intent should not unreasonably be compromised by efforts to reduce adverse events associated with treatment. Yet here too there is scope for taking measures to reduce the risk of long-term cardiotoxicity.

Given the frequency and clinical significance of CHF in anthracycline-treated cancer patients, attention has been paid to its prevention, early detection and management. Carver et al. [12] emphasise the importance of a thorough initial history and physical examination, aggressive treatment of existing cardiovascular risk factors, baseline and serial echocardiography and prompt medical management of incipient heart failure. They also emphasise that—in an era in which aggressive lymphomas are curable—the elderly should not have to accept chemotherapy with diminished efficacy. Similar thoughts are reported by Lenihan and Esteva [90] in the breast cancer setting.

Evidence of long-term toxicity has led to a sustained move towards reducing the dose of doxorubicin administered and to the establishment of limits on cumulative anthracycline exposure. A cumulative dose of 450 mg/m² of conventional doxorubicin is now taken as the point beyond which risk of cardiotoxicity limits further therapy [2]; and, at a cumulative dose of 300 mg/m², it may be prudent to attempt to reduce the potential cardiotoxicity of further exposure. Such limits are set for the overall patient population and it is possible that for elderly patients lower limits would be more appropriate. If elderly patients place fewer demands on their heart and have lower expectations about cardiac performance, they may report symptoms only when cardiac function has declined to an extent that would not be tolerated by someone younger.

In the absence of controlled studies in the elderly, close monitoring of cardiac function every 2–3 cycles of conventional anthracycline administration appears to be a cautious and reasonable monitoring procedure for patients aged 70 years or older. As in younger patients, anthracyclines should be stopped if LVEF decreases below the lower limit of normal. Moreover, measures to prevent cardiac toxicity (such as use of liposomal

### Table 4. SIOG proposals for the management of anthracyclines’ cardiotoxic risk

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

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

*Use the same method through the follow-up.
formulations, prolonged infusion or dexrazoxane) might warrant discussion either at the outset or if there is a 10% or greater drop in LVEF, even though it remains within the normal range. This consideration applies especially to patients with hypertension, diabetes or coronary artery disease.

Thus, the choice of inherently less cardiotoxic anthracycline regimens or formulations is a valuable option among elderly patients with advanced cancer who are at particular risk because of comorbidities or because pretreatment LVEF is under the lower limit of normal. Attention should also be paid to minimising risk in patients who have already been treated with a high cumulative dose of conventional anthracyclines. However, when treatment is being given with curative intent, care should be taken to ensure that reduced cardiotoxicity is not achieved at the cost of decreased efficacy.

Last but not least, physicians should keep in mind the potential for cardiovascular events during long-term follow-up.

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