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

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Abstract

A taskforce of the International Society of Geriatric Oncology (SIOG) has recently submitted recommendations on the use of anthracyclines in elderly patients. Despite the aging of the population and the high proportion of elderly individuals in the population of patients with non-Hodgkin's lymphoma, the development of specialist expertise in the treatment of elderly patients with cancer is relatively recent. Treatment of the elderly is complex because they are a highly heterogeneous population, with large variations in health status, comorbidities and life expectancy. In addition, these patients are generally more susceptible than young patients to the cardiotoxic effects of anthracyclines. Strategies for assessing elderly patients with cancer, reducing the risk of congestive heart failure, and assessing the cardiotoxic effects of treatments are discussed. In addition, a summary of the SIOG recommendations is presented.

Introduction

The International Society of Geriatric Oncology (SIOG) has the aim of fostering the development of health professionals in the field of geriatric oncology, in order to optimize treatment for older adults with cancer. A SIOG taskforce has recently submitted recommendations on the position and use of anthracyclines in elderly patients. This paper discusses some of the issues in treating cancer in the elderly, and in using anthracyclines, and presents a summary of the SIOG recommendations for their use.

Aging of the population

Across the world, the number of elderly people in the population is growing, and the median age of populations across the world is projected to increase markedly over the next 40 years.[1] A large proportion of cancers are more common in elderly than in younger patients [approximately half of non-Hodgkin's lymphomas (NHL) occur in patients older than 65 years of age; Figure 1].[2] Thus, with an aging population, the incidence of these cancers is likely to grow. Moreover, treatment of elderly patients with cancer is not a simple matter, as they are a highly heterogeneous patient population.[3] In addition, elderly patients generally have greater cardiac risk than those who are younger. There is therefore the need to develop specialist expertise in the treatment of elderly cancer patients.

History of geriatric oncology as a specialism

Interest in the treatment of cancer in the elderly is a relatively recent specialism.[4] It first crystallized at the meeting *Perspectives on Prevention and Treatment of Cancer in the Elderly,* convened by the National Cancer Institute and National Institute on Ageing in 1983. During the past 28 years, a great deal of progress has been made. This included the Venice statement about poor treatment of cancer in the elderly in 1990,[5] the publication of the first edition of *Comprehensive Geriatric Oncology* in 1998, formation of SIOG in 2000, publication of guidelines on the treatment of geriatric patients with cancer,[6,7] publication of the SIOG guidelines on comprehensive geriatric assessment[8] and, in 2010, the first publication of the *Journal of Geriatric Oncology*.

The evidence base for treatment of elderly patients with cancer

Until recently, only a minority of elderly patients with cancer were enrolled in clinical trials. In the Southwestern Oncology Group trials between 1993 and 1996, overall only 22% of patients were at least 65 years of age, and only 8-13% of patients were aged 70 years or more. This discrepancy was particularly noticeable in some conditions that affect the elderly, such as lymphoma.[9] This practice has changed somewhat in the last decade, and there are now more and more randomized, controlled clinical trials specifically in elderly patients,[10] which can form the basis of evidence-based guidelines (Figure 2).[4]

Definition and assessment of elderly patients

The definition of *elderly* is often given as a cut-off age for patients of 65 years. However, this *pension age* definition is too simplistic. As individuals age, depending both on their genetic background and on the number of insults their body has been subjected to, they age more or less well. Thus, 'the elderly' are a highly heterogeneous population.[3] Patients of the same chronological age have different levels of fitness, comorbidities, and life expectancy. This obviously has an effect on treatment decisions, particularly when using toxic therapies. To take into account this heterogeneity, and the factors that contribute to it, patients may undergo a comprehensive geriatric assessment, which evaluates patients on several domains of aging: cognition, comorbidities, emotional conditions, function, geriatric syndromes, nutrition, pharmacy, and socioeconomic conditions.[6]

The Comprehensive Geriatric Assessment (CGA) is a well established tool for assessing elderly patients to establish their health status, and risks of morbidity, mortality, and toxicity.[11] However, it is currently unclear to what extent this assessment might help to identify patients who would benefit from chemotherapy with anthracyclines. The assessment can help describe how fit a patient is, but some patients simply will not tolerate the chemotherapy, and it is difficult to identify these patients before treatment.[12] Nevertheless, it is still worth assessing patients stringently. If an elderly patient has not been fully assessed, some issues, in addition to the cancer, may be missed that would affect their outcomes over the next few years. Moreover, it has been demonstrated that interventions dictated by a CGA of the patient reduced morbidity and mortality in patients at risk of frailty.[13]

Health status or fitness as a guide to treatment in the elderly

The concept of health-status categories may be useful in predicting the life expectancy of patients. In a study of cancer screening, elderly patients were divided into three groups according to their health

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status: the top quartile were defined as those who were fit, the middle two quartiles as those with median health status (who had some minor health problems), and the bottom quartile as those who were frail, and had severe health problems.[14] The group of patients who were 80 years old and fit had a median life expectancy of a further 10.8 years, compared with 3.3 years for those who were frail. This prognosis might well affect the type of treatment a patient may be given, and the decision of whether to give adjuvant therapy in an attempt to prolong survival. However, there are currently few clinical trial data on the efficacy and tolerability of adjuvant treatments in patients who are 80 years old, so it is extremely difficult to make evidence-based treatment decisions in this patient population.

Decisions on the types of treatments elderly patients receive can be based on a general assessment of their health status and *fitness*. Elderly patients who are fit, or those who have some problems that can be ameliorated by an intervention, should in principle receive the same treatment as that given to younger patients. Those who have a worse health status and multiple problems that cannot be easily improved should be given a geriatric-specific intervention – i.e. they may receive some non-aggressive and/or palliative treatment. Despite these general guidelines, it is difficult to judge which categories patients fall into and the most appropriate treatment strategy for an individual.

Factors limiting chemotherapeutic treatment of the elderly

There are some true limitations to the use of cytotoxic chemotherapy in the elderly. A key one is renal function, as many of the drugs are excreted renally and may produce toxicity problems when used in the elderly. Other issues include liver function, drug distribution, and absorption, marrow reserves, and neurological factors.[3] In addition, elderly patients are commonly taking several different drugs, some of which may have potentially dangerous interactions, so these must be considered before treatment. Despite these limitations, there is now evidence for the benefits of chemotherapy in elderly patients with lymphoma, as discussed elsewhere in this issue (see Burchardt and Gisselbrecht in this supplement).

Anthracycline-associated cardiotoxicity

Cardiotoxicity is a known complication of anthracycline use, not only for elderly patients. Anthracyclines produce cardiotoxicity through oxidative stress, causing multiple irreversible and cumulative damage to myocytes. This can lead to rare acute toxicities, and more often to dilated cardiomyopathy, which has an insidious subclinical onset, resulting in systolic dysfunction and left-sided congestive heart failure (CHF). There are some treatments that can be used to palliate this condition, but it can lead to severe morbidity and death in some patients.[15,16]

Cardiotoxicity in elderly patients

Cardiomyopathy as a result of doxorubicin therapy has a worse outcome than idiopathic cardiomyopathy.[17] In addition, elderly patients are more susceptible than younger ones to the cardiotoxic effects of anthracyclines, because their hearts have probably already received damage, so they are more likely to develop heart failure at lower cumulative doses of doxorubicin.[18] Cardiotoxicity is a particularly marked problem in patients who have received adjuvant chemotherapy for breast cancer,[19] as the development of cardiac problems in the future may outweigh the benefits of the initial treatment. In this context, curative treatment for NHL is quite analogous to the adjuvant treatment of breast cancer.

Recognizing cardiotoxicity in elderly patients

There are several reasons why it is diffi-

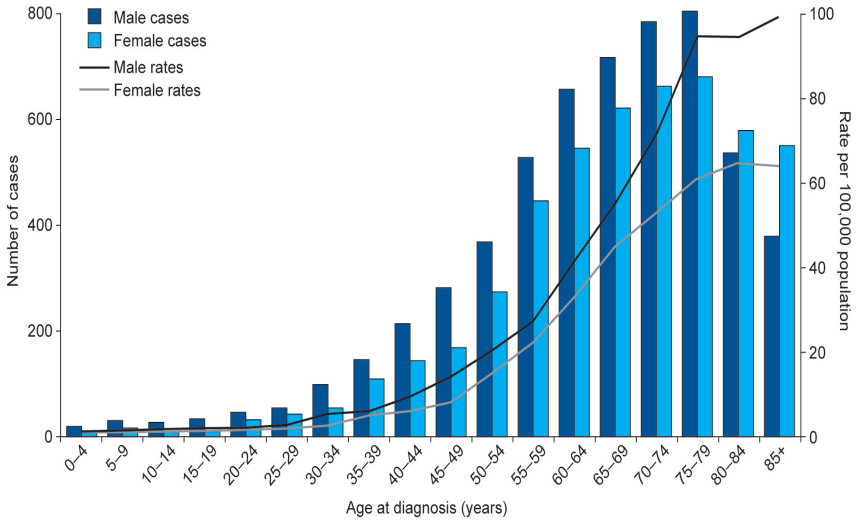

Figure 1. Number of cases and rate of hematologic disorders and solid tumors per 100,000 population, by patient age at diagnosis.[2] Reprinted with permission from Cancer Research UK, http://info.cancerresearchuk.org/cancerstats/types/nhl/incidence, October 2010.

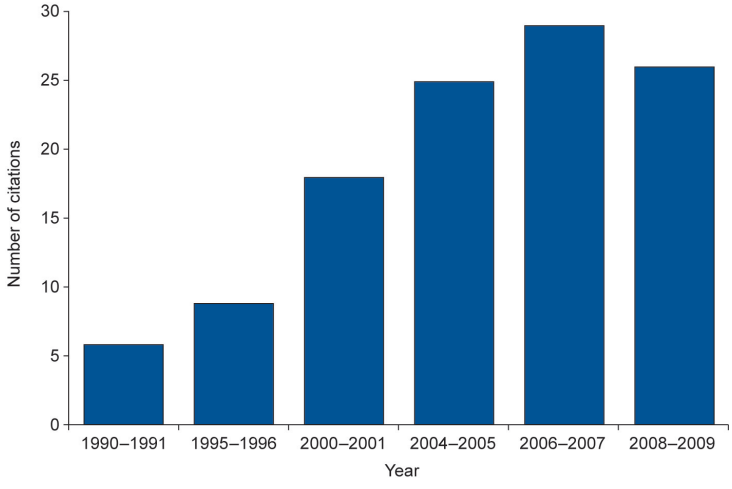

Figure 2. Number of randomized, controlled clinical trials in elderly patients (>65 years of age) with cancer over the past 20 years (using the Medline search terms: cancer/elderly; title/abstract; +65; randomized controlled trial).[4] Reprinted from Aapro MS. Launching the Journal of Geriatric Oncology: a historical milestone. J Geriatr Oncol 2010;1:2-3, ©2010 with permission from Elsevier.

cult to recognize either pre-existing or anthracycline-related toxicity in elderly patients. In general, physicians may not reliably recognize common adverse effects of chemotherapy.[20] In addition, elderly patients often have several non-treatment-related symptoms that may mask or mimic the symptoms of CHF. The classic CHF symptom triad of dyspnea, lower extremity edema, and fatigue are all common in the elderly for a number of reasons (e.g. presence of chronic obstructive pulmonary disease, obesity, drug-induced or vascular edema, cirrhosis, sleep apnea, or cancer) in addition to heart failure. Thus, it can be difficult to identify the cause of symptoms and signs. In addition, patients may not report new symptoms to their clinicians, because they consider them part of their chemotherapy or underlying disease.

There are several potential indicators of cardiac damage in patients given cardiotoxic treatments. Some studies have indicated that changes in troponin I immediately and after chemotherapy predict left-ventricular dysfunction.[21] However, other research groups have argued that this is not the most appropriate measure.[22] Brain natriuretic peptide, which is a marker of volume overload, may also be an effective marker of subsequent myocardial damage.[23] Another approach is to measure cardiotoxicity using echocardiography or multi-gated acquisition (MUGA) scans. Many cardiologists favor the use of left ventricular ejection fraction (LVEF) to monitor cardiotoxicity.[24] However, this measure is limited by the fact that it is not sensitive, and produces different measures of LVEF depending on the cardiologist conducting the examination. Moreover, these tests only detect cardiotoxicity once it has occurred and manifested as left ventricular dysfunction, whereas blood tests may detect cardiotoxicity at an earlier stage.

Reducing the risk of congestive heart failure

There are several strategies for reducing the possibility of cardiotoxicity. Dexrazoxane is a chelating agent that has been shown to reduce doxorubicin-associated cardiomyopathy and is available for this use in some countries.[25] Antioxidants have also been considered as preventive agents, but there is little evidence that these are effective. Once the first signs of toxicity are observed, early intervention with angiotensin-converting enzyme (ACE) inhibitors and possibly beta blockers may help these patients. An alternative strategy is not to treat cardiotoxicity once it has developed, but to use anthracyclines that are not cardiotoxic, which provide the same efficacy, but a reduced or no risk of long-term cardiotoxicity. The use of liposomal anthracyclines has been shown to reduce the cardiotoxicity of anthracycline treatment, compared with the conventional forms.[26]

SIOG recommendations for anthracycline use in elderly patients[27]*

Before treatment

- Recommend rigorous screening to exclude patients at unacceptably high cardiac risk (level 1a evidence).
- Propose taking a comprehensive patient history, comprising current signs or history of CHF, cardiovascular comorbidity (i.e. hypertension, diabetes, or coronary artery disease), and prior exposure to anthracyclines for this or previous malignancy (all level 1a).

Anthracycline treatment

- Recommend that clinicians do not exceed the recommended upper cumulative dose (level 1a).
- Propose a reduction in maximum cumulative dose (level 5).
- Recommend using a less cardiotoxic therapy (level 1a).
- Propose possible ways of reducing the level of cardiotoxicity:
  - use of continuous infusion (level 1a)
  - use of epirubicin (level 1a)
  - use of dexrazoxane (level 1b, level 5 in the elderly)
  - use of liposomal anthracycline formulations (level 1b, level 5 in the elderly)
  - sequential administration of conventional anthracyclines and trastuzumab in human epidermal growth factor receptor-2-positive breast cancer (level 1b, level 5 in the elderly).

Monitoring of cardiotoxicity

- Recommend regular monitoring of cardiac function, signs, and symptoms (level 1a).
- Propose measurement of LVEF by ultrasound (preferred, level 5) or MUGA scan (use the same method through follow-up) every 2-3 cycles of anthracyclines (level 1a).
- Propose:
  - special attention needed if drop in LVEF exceeds 10%, even if remaining within normal range (level 5)
  - long-term follow-up (level 1a).

Managing cardiac risk

- Recommend interventions to reduce cardiovascular risk (level 1a).
- Proposed ways to achieve this:
  - 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).

Recommendations reprinted from Aapro M et al. Anthracycline cardiotoxicity in the elderly cancer patient: a SIOG expert position paper. Ann Oncol 2011;22:257-67, by permission of Oxford University Press.[27]

Level 1a evidence: systematic review of randomized clinical trials; Level 1b evidence: individual randomized clinical trial; Level 5 evidence: expert opinion without explicit critical appraisal, or based on physiology, bench research, or first principles.

Conclusions

The treatment of elderly patients with cancer is a complex area. There is currently insufficient evidence to allow the application of specific regimens in geriatric oncology, and the impact of old age on cardiac problems is complex and poorly understood. It is important to refine treatment algorithms for older patients to ensure they receive optimal therapy. In addition, when using highly effective drugs such as anthracyclines, it is necessary to take into account the patient's status and keep in mind their best interests, particularly in terms of their long-term life expectancy. Effective and practical assessment tools are needed to realize this vision.

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