Progress in Pediatric Cardiology 39 (2015) 71–75

Contents lists available at ScienceDirect

Progress in Pediatric Cardiology

journal homepage: www.elsevier.com/locate/ppedcard

Cardiac toxicity in the elderly and the role of cardio oncology

Joseph R. Carver *

Abramson Cancer Center of University of Pennsylvania, Philadelphia, PA, United States

ARTICLE INFO

Available online 13 October 2015

Keywords:
Cardiac toxicity
Elderly
Cancer
Cardio oncology

ABSTRACT

The world population is aging and 60% of all cancer diagnoses and 70% of all cancer mortality occur in patients greater than 65 years of age. The elderly have multiple medical and non-medical comorbidities that accompany changes in pharmacokinetics and pharmacodynamics and poly-pharmacy that all impact their treatment. The elderly derive benefit from cancer treatment but are often denied chemotherapy or are undertreated based on age. Treatment decision should be based on physiologic rather than chronological age and there is a need for inclusion of more elderly patients in cancer clinical trials.

The population of the world is aging. In 2013, one of every five adults in the United States was older than 65 years and people 80 years of age and above were the fastest growing segment of that population. With this, 60% of all cancer diagnoses and 70% of cancer mortality occur in patients older than 65 years [1]. The elderly cancer patient thus presents with disproportionate numbers and presumed disproportionate risk with outcomes that may be less favorable than their younger counterparts. They are nearly absent and always underrepresented in cancer clinical trials so that there is a paucity of evidence-based guidelines. We know a lot about getting old and not a lot about treating the elderly population with cancer.

In this manuscript, the following issues will be discussed:

Who are the elderly and are they different from their younger counterparts?
How do we assess the elderly to accurately predict overall survival and the risk of developing cardiac toxicity?
What do we know about treating elderly women with breast cancer and the risks of anthracycline and trastuzumab-induced cardiac toxicity?
Is there an increased risk of anthracycline-induced cardiac toxicity when treating the elderly patient with lymphoma?
Where can cardio oncology help in treatment decisions to optimize cancer outcomes?
What are the gaps and how can we help to fill them?

1. What is Cardiac Toxicity and the Scope of This Manuscript?

Chemotherapy and radiation have acute and late effects on the heart. The related toxicity may include arrhythmias and conduction abnormalities, myocardial, valvular, and pericardial and coronary artery abnormalities. These effects have been well described [2] and will not be the focus of this manuscript. However, to illustrate the potential problems in the elderly, discussion will be directed toward asymptomatic and symptomatic left ventricular dysfunction/heart failure (HF) associated with the anthracyclines and trastuzumab. Additionally, discussion will be limited to the direct effects on the myocardium with no focus on the indirect hemodynamic changes (blood pressure, volume, electrolytes and renal function changes) that may accompany chemotherapy with acknowledgment that the elderly may be more sensitive to these indirect effects because of underlying changes in pharmacokinetics, renal and hepatic function.

2. What Does Elderly Mean and How Are They Different?

The Oxford English dictionary defines elderly "as having lived a long time: no longer young." Others define it chronologically (age > 70 years) and subcategories exist (<75 years "young old", >75 years "medium old," and >85 years "oldest old"). This is often coincident with a period of accelerated decline in physical functioning with additional definitions based on physical function (robust, normal frail). In assessment and ultimate decision making, this has to be interpreted in view of hard data from the Organization for Economic Cooperation and Development (OECD) average life expectancy of 80.1 years (81 years in women and 79 years in men) and with the ability for populations to predict remaining years of life (e.g., a 75 year old female with no co-morbidity has an average predicted life expectancy of 15 years). Tables are readily available for males and females and Fig. 1 below shows the life expectancy for women with percentiles proportional to associated co-morbidity that can be calculated individually using one of many life expectancy calculators readily available on line (e.g., http://gosset.wharton.upenn.edu/mortality/perl/CalcForm.html). The take-home message is that assessment of the elderly should not just be based on chronological

* Corresponding author.
E-mail address: Joseph.Carver2@uphs.upenn.edu.

http://dx.doi.org/10.1016/j.ppedcard.2015.10.003
1058-9813/

age and has to take into account physical function and projected remaining years of life.

Decision making in the elderly is also based on knowledge of how they are physiologically different with regard to age-related changes in host factors (organ function, DNA repair and co-morbidity), pharmacokinetics, pharmacodynamics and cancer characteristics.

A major consideration in the elderly is the presence of co-morbid conditions. Multiple studies consistently show that the number of co-morbid conditions increase with advancing age. In addition to cancer, the most common conditions include hypertension, diabetes, coronary artery disease, cardiovascular disease in general, chronic obstructive lung disease and psychiatric conditions, the latter dominated by depression. All of these naturally lead to polypharmacy that is an additional co-morbidity. All contribute proportionately to an increase in the frequency of hospitalization. It is estimated that 70% of Americans 80 years and older have at least two co-morbid conditions. In the end, these are become competing causes of death and are often potentially more lethal than the diagnosed cancer: all of these factors impact and complicate treatment decisions.

There are well defined age related changes in organ function and reserve with declining GFR and reduced hepatic metabolism. Not only is reduced hepatic drug metabolism and renal drug elimination due to an age-related decrease in GFR, but absorption, distribution and altered tissue sensitivity lead to enhanced drug effects in the elderly compared to their younger counterparts. After treatment, there is an increased susceptibility of normal tissue to the toxicity of treatment — DNA repair may be slower and the biological characteristics of the tumor and resultant drug sensitivity may not be the same as the young. For example, in diffuse large cell lymphoma, the most common lymphoid malignancy, 40% of cases occur in patients >70 years of age. In this population, the intrinsic biological properties of the tumor effect prognosis and response to therapy. The prognostically more favorable Germinal Center B Cell Like (GCB) origin is less common while the less favorable Activated B Cell Like (ABC) is more common in the elderly compared to a younger lymphoma population [3].

The elderly also suffer from an age bias. They are less likely than their younger counterparts to receive standard and effective chemotherapy and when they are treated, they often receive less than the standard dose — either at the outset or because of early side-effects of treatment. In a recent analysis of 5489 patients with Stage III colon cancer over the age of 75 years, utilization of chemotherapy decreased with advancing age and co-morbidity [4]. In that same meta-analysis from 4 large data bases, under-treatment occurred in the face of a documented survival benefit attached to treatment.

The paradox is that there is an age bias leading to under-treatment and there is a recognized survival benefit with treatment. How can this happen? It is partially due to the lack of evidence-based information that can be consistently applied to the elderly: they are underrepresented in cancer clinical trials and even when enrolled, virtually no one over the age is 80 years is included and the patients actually enrolled are subject to a bias that selects the fit, healthy who lack co-morbidity and they do not represent the overall population. Finally, the elderly who actually enroll in clinical trials are also less likely to complete those trials.

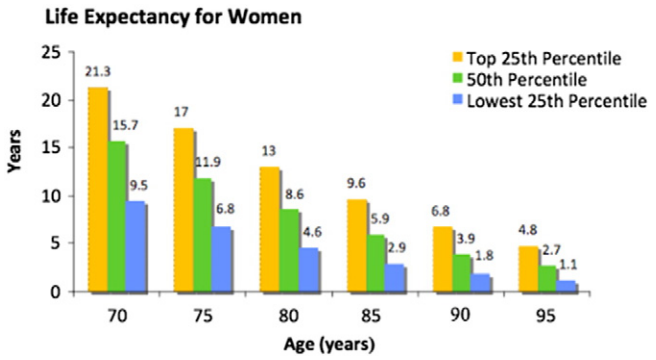

Fig. 1. Life expectancy for women.

3. How do we Assess the Elderly?

All of these factors have led to an increased interest in formal or comprehensive geriatric assessment (CGA). Traditionally, assessment of the elderly patient was based on chronological age, tumor biology and the patient's performance status as assessed by either the Karnofsky Scale or ECOG Performance Status. Both of these simple and universally adopted scores are based on easily assessable functional status and the ability to engage in self-care. There are dozens of other more formal and detailed assessment tools that take into account in variable degrees, nutritional assessment, co-morbid medical conditions, polypharmacy, cognitive function, psychological state and the presence or absence of social support in addition to age and functional status. Some examples of commonly employed CGA tools include the Charlson Index, Cumulative Illness Geriatric Assessment (CIRS), Comprehensive Geriatric Assessment, Index of Coexistent Diseases (ICD), Adult co-morbidity Evaluation-27, Kaplan Feinstein and a lymphoma specific International Prognostic Index (IPA). Succinct cardiac variables are limited and often not specifically part of the assessment (other than as a co-morbidity). All have the benefit of feasibility in all settings and offer some degree of objectivity. They identify issues previously unknown to the treatment team and can identify specific areas to target for intervention. Results predict treatment related toxicity, morbidity and mortality and may help in guiding treatment decisions and treatment selection and those patients too frail and vulnerable to undergo aggressive treatment with curative-intent. Gaps include the lack of a "gold-standard," the extended time required to complete the assessment and for overall predictive accuracy, single independent variables may be just as accurate. For example, baseline cognitive function and physical performance status each independent predicts AML survival i.e., a more simple assessment tool may have the same predictive value as a detailed and time consuming tool. In addition, there is a lack of a standard uniform approach to classifying fit vs. vulnerable vs. frail-none have been validated in RCTs and all only assess cardiac risk as a minor variable. The screening tool recommendations of the International Society of Geriatric Oncology have been recently published [5].

Take home points regarding how the elderly are different include a greater prevalence of impaired functional status and co-morbid medical conditions with a disproportionate number of psychosocial needs. This is a heterogeneous population — chronological age is uniform, aging is not so. Calendar age is less relevant than "biological" or functional age. In the end, statements about the best treatment after assessment are based in little or no clinical trial evidence.

4. Chemotherapy Issues in the Elderly

Using case vignettes, the following questions will be addressed:

1. Is the risk of chemotherapy-induced cardiac dysfunction increased in the elderly?
2. Do the elderly receive a benefit from chemotherapy compared to the non-elderly population?
3. Is there a population of elderly that is at a high risk for cardiac toxicity compared to a younger cohort?

We have established that there are physiologic and pharmacologic changes that make the elderly different from their younger counterparts. With this knowledge, it is impossible to make all-inclusive statements about the cardiac risks of chemotherapy in this population. Just as there is marked heterogeneity in the elderly, there is marked