

# ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

## Dosing Drugs in Elderly Patients With Cancer



Arti Hurria, MD  
 George Tsai Family Chair in Geriatric Oncology  
 Professor, Department of Medical Oncology & Therapeutics Research  
 Director, Center for Cancer and Aging  
 City of Hope  
 Duarte, California

### H&O What is the rate of cancer in older patients?

**AH** Almost 60% of new cancer diagnoses and 70% of cancer deaths occur in patients older than 65 years. Currently, the largest increase in cancer incidence is in patients who are 65 years or older. This rapid growth is attributable to several factors. Cancer is a disease associated with aging, and the US population is growing older. In 2011, the baby boomer population started to turn 65 years old. From 2010 to 2030, the incidence of cancer is expected to increase by 67% among people older than 65 years. In comparison, the incidence will increase by 11% in patients who are younger than 65 years.

### H&O How do treatment goals differ in older patients vs younger patients?

**AH** The goal of therapy weighs heavily in management decisions, regardless of the patient's age. All patients want to know whether the treatment is curative or palliative. A survey published in the *New England Journal of Medicine* evaluated treatment goals of older adults with chronic illnesses, including cancer. The survey found that the vast majority of older adults would forego a potentially life-saving treatment if it impacted cognition or function. A study from City of Hope, led by Dr Enrique Soto-Perez-de-Celis, that focused on older patients with cancer found similar data. Most patients surveyed would rather forego treatment than lose their mental capacities.

Patients of all ages want to understand the impact of a treatment on disease-free survival and overall survival, the standard endpoints measured in clinical trials. However,

other factors also weigh heavily in the decision-making process for older adults, such as the impact of treatment on function and cognition.

Another observation from my clinical practice is that older patients consider how treatment will impact their caregivers, particularly their children. Often, patients do not want to bother their children. In addition, the patient may be a caregiver for someone else. Patients are always thinking about how treatment will impact their caregivers or their own ability to care for other people.

### H&O How do cancer treatments impact the aging process?

**AH** This is an area of active study. I am the chair of a National Cancer Institute steering committee that is evaluating key research gaps and opportunities for how cancer treatment accelerates the aging process. Compelling data from studies in younger patients who survive childhood cancer demonstrate an increased risk of frailty and other medical problems compared with individuals without a history of cancer. In clinical practice, we see that cancer treatments can impact the aging process. Current research is exploring whether it is possible to predict the long-term side effects of treatment, identify patients at risk, and mitigate the risk.

### H&O Do pharmacokinetics and pharmacodynamics differ in older patients?

**AH** Studies that have evaluated the pharmacokinetics of cancer therapies with age found modest age-related differences. In contrast, several studies have found age-related differences in pharmacodynamics, with older adults at

increased risk for adverse events from cancer treatment. However, this risk is heterogeneous among individuals of the same chronologic age. Therefore, it is important to understand the patients' functional age (in comparison with their chronologic age) when making treatment decisions. A geriatric assessment can help in this regard.

### **H&O** What are the components of a geriatric assessment?

**AH** A geriatric assessment evaluates domains other than age that can predict the risk of morbidity and mortality. These domains include functional status, comorbid medical conditions, nutritional status, cognition, psychological state, social support, use of other medications, and evidence of interactions among medications.

### **H&O** Should all older patients undergo geriatric assessment?

**AH** New guidelines from the American Society of Clinical Oncology recommend a geriatric assessment for all patients undergoing chemotherapy who are age 65 and older. The assessment should be performed at diagnosis, when the treatment plan is being devised, and can be repeated at times when the patient's health status changes and new treatment decisions need to be made. The items in the assessment can provide insight into a patient's areas of vulnerability, and hence can lead to the development of rational interventions to decrease the risk. The assessment can be repeated several times throughout treatment to identify any changes in the patient's status.

The geriatric assessment can identify practical issues that impact treatment. For example, if patients lack transportation, that would trigger the question of how they will get to their doctor's appointment or how they would seek medical attention if they developed a severe side effect. If a patient has lost weight, a nutritional consult might be indicated. If the patient lives alone, it might be helpful to connect him or her with a social worker. A patient who falls frequently might require rehabilitation.

The Cancer and Aging Research Group created a calculator based on results from the geriatric assessment that can estimate a patient's risk for severe adverse events, meaning grade 3 (hospitalization), grade 4 (admission to an intensive care unit), and grade 5 (treatment-related mortality). The toxicity calculator was developed in a cohort of 500 patients and then validated in another 250 patients. Risk is calculated based on 11 items, such as tumor type, treatment, laboratory values, and geriatric assessment questions. The calculator is available at the Cancer and Aging Research Group website, [www.mycarg.org](http://www.mycarg.org), and is translated into several different languages.

### **H&O** What factors might prompt consideration of a planned dose reduction of chemotherapy during the first cycle?

**AH** It depends on the intent of treatment. If a patient is receiving adjuvant treatment with curative intent, then the typical practice is to start with the standard dose. In this setting, a change in the dosing might compromise the cure. If the full dose leads to adverse events of grade 3 or 4, then a dose reduction might be considered. In a setting where the treatment is palliative, however, it may be preferable to start low and go slow, meaning start the first dose lower and then dose escalate if the patient is doing well. This strategy was evaluated in the FOCUS2 trial (Chemotherapy Options in Elderly and Frail Patients With Metastatic Colorectal Cancer) in gastrointestinal malignancies, and it appeared to be a good strategy.

### **H&O** What are the signals that an older patient may benefit from a different drug dose after treatment has started?

**AH** A change in the dose should be considered if the patient develops an adverse event of grade 3 or higher according to common toxicity criteria from the National Cancer Institute (NCI). However, even some grade 2 toxicities are significant in older adults, and may require a dose reduction or change in therapy. For example, grade 2 neuropathy that impacts a patient's instrumental activities of daily living could have devastating consequences by decreasing the ability to live independently and increasing the risk for falls. The chance that an adverse event will persist for the long-term should raise the possibility of changing treatment.

As mentioned, we developed and validated a chemotherapy toxicity calculator and established the feasibility of performing a geriatric assessment in patients enrolled in clinical trials and in clinical practice. We then questioned whether a multidisciplinary team can develop an effective intervention strategy when the assessment identifies areas of vulnerability. We are currently undertaking a randomized controlled trial to see whether interventions driven by geriatric assessment can improve the care of older adults with cancer by decreasing their risk of adverse events. The process under study is as follows: a nurse-led team with expertise in geriatric care evaluates the patient with a geriatric assessment, and inputs values into the chemotherapy toxicity calculator. Then a multidisciplinary team meets, reviews those results, and outlines appropriate interventions. For example, should a patient who falls frequently see a rehabilitation specialist? Should a depressed or anxious patient see a psychologist or psychiatrist? We then send the results of the assessment and the recommended

interventions to the patient's doctor. We ask the doctor if we can implement these interventions and follow the patient throughout the chemotherapy course. The trial will address several questions. For example, does the intervention decrease the risk of severe toxicity and hospitalization? Does the intervention improve the number of patients who have completed an advance directive? Are we able to help patients maintain function throughout treatment?

### **H&O** Does it appear that targeted therapies will be dosed differently in older patients?

**AH** This important area is a focus of active research. As targeted therapies emerge as the standard of care in many different tumor types, it is critical to assess the potential side effect profile, which might differ in older adults.

### **H&O** Why are older adults underrepresented in clinical trials?

**AH** The challenge is multifactorial, involving provider, system, and patient barriers. I am mentoring my colleague Dr Mina Sedrak, who is leading research in this area. He is seeking to improve the accrual of older adults to clinical trials. In addition, there is a need for age-specific studies. It is necessary to understand the unique side effects that arise in older adults and to modify clinical trials with additional safety criteria that incorporate close monitoring throughout treatment.

### **H&O** How else can clinical trials be modified for older patients?

**AH** There are several ways to modify trial design to accommodate the needs of older adults. The Cancer and Aging Research Group, in collaboration with the National Institute on Aging and the NCI, held a series of conferences funded by a U13 grant to identify and address gaps in knowledge in the care of older adults with cancer. The group has published several white papers, including one focused on how to modify therapeutic clinical trials for older adults with cancer. One promising, innovative way would apply to trials evaluating whether drug A plus B is better than drug A plus C. Say that the trial finds that drug A plus B is more efficacious than the other arm, but that older adults were underrepresented in the study population. We would recommend that the study include an expansion cohort to evaluate the more efficacious treatment in older adults to identify any unique side effects and understand the feasibility of delivering the treatment.

### **H&O** Do you have any other insights into the management of older patients with cancer?

**AH** To young oncologists who are deciding on a career path, I would say that geriatric oncology is an incredible career path with the opportunity to take care of wonderful patients who are vulnerable and really need champions. It is an absolute joy to care for these patients, in terms of both the love they give and the personal satisfaction derived. These patients have incredible wisdom about life to share. In addition, although this patient population represents the majority of cancer cases, they have been underrepresented in cancer research. Therefore, to move forward in cancer research with advances that will impact the majority of patients, studies in geriatric oncology are needed. More studies of older patients will be able to help so many people, both nationwide and worldwide.

### **Disclosure**

*Dr Hurria has received research funding from Celgene, Novartis, and GlaxoSmithKline, and has served as a consultant for Boehringer Ingelheim Pharmaceuticals; Carevive; Sanofi; GTx, Inc; Pierian Biosciences; and MJH Healthcare Holdings, LLC.*

### **Suggested Readings**

Freedman RA, Dockter TJ, Lafky JM, et al. Promoting accrual of older patients with cancer to clinical trials: an Alliance for Clinical Trials in Oncology member survey (A171602) [published online April 19, 2018]. *Oncologist*. doi:10.1634/theoncologist.2018-0033.

Fried TR, Bradley EH, Towle VR, Allore H. Understanding the treatment preferences of seriously ill patients. *N Engl J Med*. 2002;346(14):1061-1066.

Hurria A, Dale W, Mooney M, et al; Cancer and Aging Research Group. Designing therapeutic clinical trials for older and frail adults with cancer: U13 conference recommendations. *J Clin Oncol*. 2014;32(24):2587-2594.

Hurria A, Levit LA, Dale W, et al; American Society of Clinical Oncology. Improving the Evidence Base for Treating Older Adults With Cancer: American Society of Clinical Oncology Statement. *J Clin Oncol*. 2015;33(32):3826-3833.

Hurria A, Mohile S, Gajra A, et al. Validation of a prediction tool for chemotherapy toxicity in older adults with cancer. *J Clin Oncol*. 2016;34(20):2366-2371.

Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol*. 2011;29(25):3457-3465.

Mohile SG, Dale W, Somerfield MR, et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. *J Clin Oncol*. 2018;36(22):2326-2347.

Mohile SG, Magnuson A, Pandya C, et al. Community oncologists' decision-making for treatment of older patients with cancer. *J Natl Compr Canc Netw*. 2018;16(3):301-309.

Seymour MT, Thompson LC, Wasan HS, et al; FOCUS2 Investigators; National Cancer Research Institute Colorectal Cancer Clinical Studies Group. Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial. *Lancet*. 2011;377(9779):1749-1759.

Soto Perez De Celis E, Li D, Sun C-L, et al. Patient-defined goals and preferences among older adults with cancer starting chemotherapy (CT) [ASCO abstract 10009]. *J Clin Oncol*. 2018;36(15 suppl).

Soto-Perez-de-Celis E, Li D, Yuan Y, Lau YM, Hurria A. Functional versus chronological age: geriatric assessments to guide decision making in older patients with cancer. *Lancet Oncol*. 2018;19(6):e305-e316.