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Arti Hurria, M.D.: A tribute to her shining legacy in the Alliance for Clinical Trials in Oncology☆

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Early in her career, while still a holder of a K23 Paul B. Beeson Career Emerging Leaders Career Development Award in Aging, Arti Hurria, M.D. recognized the need to devote her career to studying how to provide the best cancer care to older patients. This rapidly growing cohort currently comprises approximately 70% of patients with cancer [1]. Within the Alliance for Clinical Trials in Oncology, Dr. Hurria's contributions to the field of geriatric oncology were extensive and can perhaps be categorized with the following rubrics: 1) further development and dissemination of the oncology geriatric assessment, 2) collaborative leadership in efforts that enabled investigators to delve into specific clinical care issues in older patients with cancer, and 3) the development and initiation of a clinical trial that serves as a prototype for investigating how older patients tolerate newly-approved, novel cancer agents.

Here we expound upon some of Dr. Hurria's paradigm-shifting work that has changed cancer care for older patients for the better. We focus primarily on work that was conducted within the Alliance for Clinical Trials in Oncology (formerly the American College of Surgeons Oncology Group, the Cancer and Leukemia Group B, and the North Central Cancer Treatment Group). This piece serves as a tribute to this investigator's legacy as a medical oncologist, geriatrician, researcher, mentor, collaborator, and leader.

1. The Geriatric Oncology Assessment

1.1. The Recognition of the Need for an Oncology Geriatric Assessment

One of Dr. Hurria's most important contributions is the development of a tool to assess the risk of cancer treatment among older patients. She boldly challenged the then-current-dogma that chronological age and performance status are sufficient predictors of tolerance of cancer therapy and overall survival in older patients with cancer [2–7].

In an opinion piece entitled, "We Need a Geriatric Assessment for Oncologists," Dr. Hurria explained the following [2]:

> *Oncologists typically rate a patient's functional status by assigning a Karnofsky or Eastern Cooperative Oncology Group performance status. This brief and relatively simple evaluation estimates tolerance to treatments and overall survival in the cancer population, but does not address the functional limitations that are predictive of morbidity and mortality in the geriatric population as a whole. A geriatrician's assessment of functional status includes an evaluation of the patient's ability to complete activities of daily living (ADLs)….and instrumental activities of daily living (IADLs). The need for assistance with these activities is an independent predictor of morbidity and mortality in the general geriatric population. Older individuals with cancer are more likely than individuals without cancer to have functional limitations in ADLs and IADLs.*

Even in 2006, when integrating the geriatric assessment into oncology was nothing more than a nascent concept, Hurria argued that a "geriatric assessment helps uncover problems that might influence the ability to tolerate cancer therapy – problems that might otherwise go unrecognized" [2]. Although 20% of older patients with cancer have an Eastern Cooperative Oncology Group (ECOG) performance score of 2, many of these patients require assistance with the completion of activities of daily living – an early warning sign of poor tolerance of cancer treatment. Indeed, Extermann and others showed that, in older patients with cancer, the correlation between healthcare provider-assigned performance score and ADLs/IADLs is moderate at best, a set of observations that underscored the need for prediction tools that can spare older patients the toxicity of cancer treatment [8]. Conversely, the literature shows that older patients with cancer are often untreated or undertreated – circumstances that point to the importance of developing prediction tools that can embolden cancer healthcare providers to treat older patients in a manner directly commensurate with their ability to tolerate antineoplastic therapy [9,10]. The development of such an assessment tool that was to be administered by healthcare personnel for oncology patients was particularly important, as not all oncology clinics have easy access to geriatric healthcare providers.

Hurria and others turned out to be correct and prolific; the oncology geriatric assessment is extremely important. And of note, she and others conducted some of her work on incorporating the geriatric assessment in patients with cancer within the Alliance for Clinical Trial in Oncology.

1.2. Demonstrating the Feasibility and Relevance of the Oncology Geriatric Assessment

Starting with a pilot study, Hurria and others recognized the importance of an initial demonstration of feasibility, particularly prior to testing the geriatric assessment within the National Clinic Trials Network (NCTN). Working collaboratively with other Alliance investigators and others, Hurria and others developed an oncology geriatric assessment in a manner that enabled such an evaluation to go beyond performance status and chronological age. This geriatric assessment embraced the domains of functional status, comorbid medical conditions, cognition, nutritional assessment, psychosocial status, and social support, all of which are important in geriatric medicine and in geriatric cancer care. Importantly, the geriatric assessment for patients with cancer relied upon previously-validated items, but, adhering to the vision of facilitating better decision-making for older patients with cancer, their families, and cancer healthcare providers, it deliberately placed a special focus on three domains. First, building on decades of oncology data on performance status, the oncology geriatric assessment placed a greater emphasis on physical function and included such testing as the Timed Up and Go. Second, patients often embark on complex cancer treatment regimens that require adherence to complicated instructions; therefore, the oncology geriatric assessment also included a measure of cognition. This emphasis on cognition also allowed for capturing baseline symptomatology that allowed for distinctions between underlying cognitive impairment and treatment-induced cognitive impairment; in the past, such data had sometimes been lacking in other cancer settings. Third, by virtue of having lived a long life and of having sometimes outlived family and friends, the older patient with cancer likely needs to rely on social support more than younger patients; thus, this newly devised oncology geriatric assessment also emphasized the need to understand the older patient's degree of social support. As Hurria and others explained many times, others investigators had already sought to develop a geriatric assessment. However, what appears to have distinguished this oncology geriatric assessment from previous assessments is its methodical query for relevant data that could directly impact cancer decision-making and its methodical goals for validation. This oncology geriatric assessment was specifically designed to be both informatively comprehensive and usefully reliable.

Although the geriatric assessment in non-cancer settings had already demonstrated its ability to reduce early re-hospitalization rates and mortality, such a track record was unestablished in older patients with cancer, especially those considered candidates for cancer therapy. Moreover, the issue of feasibility loomed large, particularly given the comprehensive nature of the geriatric assessment; among non-cancer

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geriatric patients, the geriatric assessment could take 2 h, a duration that was not feasible in a medical oncology clinic. Thus, the first foray into integrating the geriatric assessment into cancer care focused on feasibility. The latter was demonstrated in a 43-patient trial that included a wide sampling of patients with a median age of 74 years (range 65 to 87 years) with breast cancer, colorectal cancer, lung cancer, and lymphoma of all stages of disease [3]. Feasibility was clearly demonstrated: the mean time to completion was 27 min (standard deviation = 10 min; range = 8 to 45 min). Most patients (87%) completed the self-administered portion without help. The oxymoron of merging brevity and comprehensiveness was realized, thereby setting the stage for further study and development.

1.3. Further Success with Feasibility with CALGB 360401

Integrating an oncology geriatric assessment within a cancer cooperative group, or now referred to as the National Clinical Trails Network (NCTN) brought the geriatric assessment to a new level, showing nation-wide feasibility [11]. CALGB 360401 demonstrated such success. This 15-site, 95-patient (85 were assessable) trial required that the geriatric assessment be completed prior to the initiation of cancer treatment, and, in view of its ground-breaking goals, it was also effort-intensive, requiring the primary study team to identify patients by means of daily review of CALGB ongoing patient accrual records to other trials and the principal investigator's (Dr. Hurria's) role of personally providing geriatric assessment training by telephone. Of note, the trial endpoints were patient-centric, rigorous, and clearly-defined, as shown in the verbiage below from the published manuscript [11]:

> *Successful implementation would be declared if: more than 70% of patients completed the self-report patient questionnaire without assistance, and the median time to complete the entire geriatric assessment tool was fewer than 40* min. *With the aim of refining the geriatric assessment tool, a measure might be removed if: more than 25% of patients failed to answer at least one item on a geriatric assessment measure included within the tool, or more than 20% of patients reported that the measure was upsetting or difficult to understand. Also, if fewer than 80% of health care professionals completed the health care professional portion, this portion might be modified or removed from the geriatric assessment tool.*

One-hundred percent of patients completed their portion of the geriatric assessment, and 87% completed it without assistance – well exceeding the 70% target rate of success. The time to complete the testing was 15 min for patients and 5 min for healthcare providers (total time 20 min – half the 40 min threshold for success). Interestingly, 92% of patients were satisfied with the length of the questionnaire, and no major issues were repeatedly cited as problematic, leaving the tool in its original version, as it continued to be tested. In CALGB 361006, Klepin and others reported similar results in patients with acute myeloid leukemia [12].

As a result of such feasibility data from the Alliance, the oncology geriatric assessment continued to be tested in other clinical settings and continued to demonstrate value. Woyach and others integrated the oncology geriatric assessment into a high-profile trial that included 547 older patients with chronic lymphocytic leukemia; the goal of this trial was to examine the efficacy of ibrutinib, either alone or in combination with rituximab, relative to chemoimmunotherapy [13]. This practice-changing trial demonstrated that single agent ibrutinib is the standard of care. Importantly, among the 369 patients in this trial assigned to complete the geriatric assessment, 95% were able to accomplish such baseline testing. The fact that these investigators did not observe differences in baseline oncology geriatric assessment testing between the three treatment arms suggests an absence of confounding baseline characteristics between arms and underscores the value of these practice-changing trial results.

Along similar lines, Guerard and others are currently testing an electronic version of the oncology geriatric assessment (A171603). This trial examines the feasibility of testing a geriatric assessment that occurs by means of a patient's entry of data into an electronic device. The study has completed accrual but remains open to enroll patients of diverse racial and ethnic backgrounds; final results are expected in late 2019.

1.4. Using the Oncology Geriatric Assessment Beyond the Alliance

In collaboration with Dr. Hurria, the NRG conducted another trial with the oncology geriatric assessment [14]. This trial was undertaken in patients who were 70 years of age or older with ovarian cancer, enrolling a total of 212 eligible patients who were candidates for postoperative chemotherapy. Interestingly, patients' IADL scores at baseline were not associated with completion of the anticipated 4 cycles of chemotherapy in the absence of a dose reduction or therapy delay ($p = .21$). However, an association between baseline IADL scores and adverse events was observed. The odds ratio of grade 3+ adverse events diminished by 17% (OR: 0.83; 95%CI: 0.72–0.96; $p = .013$) for each additional activity for which the patient was deemed independent. Findings also suggested improved baseline IADL scores might be associated with improved survival. This prospective study points out the clinical relevance of some elements of the oncology geriatric assessment.

In general, the oncology geriatric assessment continues to be studied and integrated into the therapy of older patients with cancer. Its value continues to become manifest in a variety of clinical cancer settings [15–22].

2. Understanding Clinical Care Issues in Older Patients with Cancer

2.1. Learning from "Geriatric Assessment-Type Data."

The capture of multi-domain data, as occurs in the conduct of the oncology geriatric assessment, prompted Alliance investigators to seek an enriched understanding of issues faced by older patients with cancer, even when a more formal geriatric assessment had not been undertaken. The important trial from Muss and others (CALGB 49907) provided solid groundwork for many of these efforts [23], as did an observational study (CALGB 369901), conducted in parallel [24]. Although a formal geriatric assessment had not been undertaken in CALGB 49907, geriatric assessment-type data were generated in this trial; the analyses of such data generated illuminating conclusions.

For example, Hurria and others examined functional decline in older women who had been treated with adjuvant therapy for breast cancer as per CALGB 49907 [25]. Reporting on data derived from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, these investigators described how 42% of these older patients manifested a decline in function at some point during chemotherapy but that 47% of these patients who declined then went on to recover at 12 months. These data point to resilience among older patients, but they also underscore the importance of counseling patients with high fatigue scores, a risk factor for functional decline, about the potential for decline and the potential for struggling to recover from this decline after completion of adjuvant therapy.

As another example, Hopkins and others examined musculoskeletal symptoms in 321 older women who were receiving adjuvant chemotherapy on CALGB 49907 and reported that 87% – in effect, the vast majority – described such musculoskeletal symptomatology 2 years after the initiation of adjuvant chemotherapy [26]. These symptoms included lymphedema, limited range of motion of the arm/shoulder, and pain. Admittedly, these symptoms occurred in the setting not only of chemotherapy but also surgery and sometimes radiation. A major point is that many older patients are plagued by musculoskeletal symptoms, which are likely cancer therapy-induced, well after completion of therapy and that such symptoms merit further study because of their potential to impair the functionality of older women.

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As a third example, items from the geriatric assessment were used to estimate a frailty index that predicted long-term mortality in patients with breast cancer, in CALGB 369901, as mentioned above [27]. Adjusted hazard ratios for all-cause mortality in pre-frail/frail and robust patients were 1.7 (95% CI 1.2–2.4) and 2.4 (95% CI 1.5–4.0), respectively, with an absolute mortality difference of 23.5%. The adjusted hazard of breast cancer death was greater than 3 times higher for frail versus robust patients (absolute difference of 14%), and treatment differences did not account for these associations between frailty and mortality. These investigators concluded that most older patients with breast cancer could consider postoperative chemotherapy, as appropriate; however, pre-frail/frail patients have increased long-term, all-cause and breast-cancer mortality and should perhaps think twice about postoperative chemotherapy. These findings further underscored the clinical usefulness of the geriatric assessment to inform discussions about treatment decision-making and care planning among older patients with cancer.

The three examples above are culled from many others. Dr. Hurria provided collaborative leadership – in conjunction with Hyman Muss, M.D.; Harvey Cohen, M.D., the two co-chairs of the Cancer in the Older Adult Committee up until 2017; Aminah Jatoi, M.D. and Jennifer Le-Rademacher, Ph.D., co-chair with Dr. Hurria and Vice Chair, respectively, of the Committee starting in 2017; Jacqueline Lafky, M.S., manager of the Alliance NCI Community Oncology Research Program (NCORP) – all in an effort to enable investigators with a passion for geriatric oncology to discuss issues specific to older patients with like-minded investigators within the Alliance for Clinical Trials in Oncology and to draw and publish important conclusions that contributed to the understanding of how best to care for older patients. These endeavors served to engage a large group of junior, nationally-emerging, and well-established investigators – many of whom have contributed to this tribute – with a focus on issues germane to older patients with cancer.

These issues include quality of life of older patients during cancer therapy; older patients' self-reported cognitive function over time during cancer treatment; social support and its ramifications during the cancer journey; rates of chemotherapy-induced neuropathy in older patients; tolerating capecitabine within the context of renal dysfunction; patient preferences with respect to adjuvant chemotherapy; defining the role of doublet, platinum-based chemotherapy in older patients with lung cancer; the identification of risk factors for toxicity in older patients with hormone receptor-positive breast cancer; reasons for time-to-treatment failure in older versus younger patients with cancer; the impact of body weight-based chemotherapy dosing on cancer outcomes in older patients with breast cancer; using placebo to show that adverse event reporting is comparable in older and younger patients; details on the trajectory of frailty among older patients; the value and limitations of using ePrognosis to estimate 2-year all-cause mortality in older women with breast cancer; trends in accrual of older women with breast cancer to clinical trials; and an exposition of the role of older-patient-specific trials and their importance in geriatric oncology care [28–39].

3. Alliance A171601: the Prototype for Testing Novel Agents in Older Patients with Cancer

Alliance A171601 (current principal investigator: Mina Sedrak, M.D.; former PI: Arti Hurria, M.D.) is an ongoing clinical trial that serves as a prototype for learning how older patients with cancer tolerate new cancer drugs. This trial, "A phase II trial assessing the tolerability of palbociclib in combination with letrozole or fulvestrant in patients aged 70 and older with estrogen receptor-positive, her2-negative metastatic breast cancer" is a practical trial that relies on the geriatric assessment as well as standard adverse event criteria to assess potential functional changes related to the use of this extensively prescribed biological agent. The impetus for this study was an acknowledgement of a dearth of data on palbociclib for the treatment of breast cancer among older patients. Specifically, the package insert for this agent describes how only 37 patients in the pivotal approval trial for this drug were >/= 65 years of age and only 8 patients were >/= 75 years of age. This phase II trial is currently accruing patients and is intended to fill the knowledge gap in the use of this regimen in older patients with breast cancer, enabling the study team to acquire adverse event data that will enable clinicians to appropriately counsel older patients when offering them therapy with this drug combination. Dr. Hurria's goal was to incorporate standard of care practices, as applied to older patients in a non-clinical trial setting, to capture adverse events, and to learn how potentially to modify the dose of cancer treatment in an older group of patients. The primary endpoint of this trial is to report on the proportion of patients who develop grade 3 or worse adverse events, as per NCI common terminology criteria for adverse events (CTCAE). A unique aspect of this trial is its incorporation of the oncology geriatric assessment, patient-reported outcomes, body composition assessment, and the measurement of circulating cytokines with the goal of exploring associations between these variables and adverse events.

The successful mounting of this trial within the Alliance NCI Community Oncology Research Program (NCORP) is a seminal achievement. Moreover, this trial serves as a prototype for how to test new biologic cancer agents in a group of older patients to provide assurance that these new drugs will yield an acceptable adverse event profile in this more vulnerable group of patients with cancer. New cancer agents are now approved quickly but within the context of sample size that encompasses only a small fraction of older patients – too few to be representative of the majority of older patients who will eventually be exposed to the drug. In effect, A171601 serves as a first-step to demonstrate how similar trials with newer agents might move forward in older patients with cancer to ensure the safety of these patients.

4. The Authors' Personal Comments

The authors of this paper continue to mourn Dr. Hurria's passing and will continue to do so for a long time; these sad circumstances evoke a quotation from the Bengali poet, Tagore [40]:

> *If you cry because the sun has gone out of your life, your tears will prevent you from seeing the stars.*

Dr. Hurria provided mentorship, collegiality, collaboration, and – as co-chair of the Alliance Cancer in the Older Adult Committee – leadership to the Alliance for Clinical Trials in Oncology. Her passion to make a meaningful impact in the lives of patients with cancer endeared her to her colleagues, mentees, patients, and all others who worked with her. She created a sense of community among all who had an interest in older patients with cancer.

However, these "stars" are not only Dr. Hurria's thoughtful, rigorous, and impactful research observations, a limited group of which has been described here. Nor are these "stars" limited to the truly meaningful interpersonal interactions Dr. Hurria engendered among all. The "stars" are also, tangibly, all the Alliance investigators and other staff – early, well-established, and all in between – who serve as members of the Cancer in the Older Adult Committee, who carry on her legacy, and who continue to take geriatric oncology research to new heights with the goal of improving the care of all older patients with cancer. Dr. Hurria's legacy will shine brightly for years to come.

Conflict of Interest Statement

JF reports personal fees from AstraZeneca, Merck, Pfizer, Genentech, Takeda outside the submitted work; GK reports Scientific Advisory Boards: Boehringer Ingelheim; Eisai [Epirubicin]; Genomic Health [OncotypeDX]; Agendia [MammaPrint], Consulting/advising relationship: Genomic Health, AstraZeneca, Novartis, Pfizer, Honoraria (speakers bureau): Eisai, Research Funding: Bionovo, PUMA, Roche,

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Other: Seattle Genetics, Genomic Health outside the submitted work. VM reports other from Celgene, other from Genentech, other from Pharmacyclics, other from Seattle Genetics, other from Takeda outside the submitted work; NV resports a consulting and advisory board relationship with Vector Oncology/Concerto Health AI; TW reports other from Janssen, personal fees from Carevive outside the submitted work. JW reports personal fees and other from Pharmacyclics, personal fees and other from Janssen, other from Abbvie, other from Loxo, other from Karyopharm, other from Morphosys outside the submitted work; all other authors have no conflicts of interest to declare.

Author Contributions

All authors contributed equally to this work.

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