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Geriatric Oncology Research in the Cooperative Groups: A Report of a SIOG Special Meeting

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Abstract

Purpose—The purpose of this meeting was to bring together geriatric oncology researchers in the cooperative groups to discuss the design of clinical trials to improve our knowledge of the efficacy and toxicity of cancer therapeutics in older adults with cancer.

Design—Meeting of cooperative group leaders in geriatric oncology research

Results—Several strategies were suggested to improve our knowledge of the efficacy and toxicity of cancer therapeutics in older adults. These include: 1) developing therapeutic studies for older adults who are not eligible for standard clinical trials (because of comorbidity or functional status), or for patients who are deemed to be at high risk for toxicity from standard therapy (frail or vulnerable); 2) identifying the age group of older adults who are underrepresented on clinical trials and developing trials specifically for these patients; 3) designing trials to include a certain proportion of older adults for subset analyses; and 4) including a geriatric assessment in therapeutic clinical trials in order to identify factors other than chronologic age that identify those older adults who are “vulnerable” (at risk for toxicity) and “fit” (able to tolerate cancer therapy without significant toxicity).

Conclusions—To address knowledge gaps in geriatric oncology, national and international cooperative group leaders discussed strategies in clinical trial design to improve the evidence-based research and accrual of older adults. Linking the efforts among cooperative groups will expedite this progress, and this conference was a major first step toward this goal.

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Introduction

With the aging of the US and worldwide population and the known association between cancer and aging, the pursuit of evidence-based research in the care of older adults with cancer is becoming increasingly important. Cooperative multicenter clinical trials are seeking to establish a standard of care for the treatment of cancer, but older adults are underrepresented in these trials.¹ Older adults have also been underrepresented in research trials submitted to the US Food and Drug Administration (FDA) for consideration of new drug approval.² This dearth of evidence-based data regarding the treatment of older adults contributes to age-related variations in treatment patterns.³⁻⁹ To address this knowledge gap, national and international cooperative groups are beginning to design clinical trials that improve their evidence-based research and accrual of older adults.

In November 2008, the International Society of Geriatric Oncology hosted a conference for international leaders in geriatric oncology research. The purpose of this meeting was to bring these researchers together to share ideas and discuss the challenges in conducting geriatric oncology research. The attendees (please see Table) reviewed the ongoing portfolio of research within their cooperative groups, discussed strategies for including older adults in clinical trials, and identified areas for future research and ways to improve the accrual of older adults in these trials. This meeting report summarizes the discussions held at this conference, describes examples of successful strategies that were described, identifies gaps in the geriatric oncology research portfolio, and suggests ways to address these gaps in the future.

Strategies for Geriatric Oncology Clinical Trial Design

At the conference, a panel of cooperative-group leaders reviewed their ongoing portfolios of therapeutic research. Two main strategies for evaluating cancer treatment efficacy and tolerance in older adults were described: 1) Design clinical trials specifically for fit older adults with cancer and 2) Include a subgroup analysis of older adults enrolled in a treatment trial for patients of all ages. The need for clinical trials of “frail” or “vulnerable” patients regardless of age was also discussed. Each of these approaches is described below.

Developing Therapeutic Clinical Trials Specifically for Older Adults

The investigators identified the benefits and challenges of designing clinical trials specifically for older adults. The following were described as potential benefits of clinical trials for older adults:

1) Older adults may be particularly vulnerable for certain toxicities—Clinical trials in older adults can identify toxicity concerns that are unique to the decreasing physiologic reserve that characterizes an aging population. Older age is characterized by a decrease in organ function reserve, such as declines in renal function and bone marrow reserve.^{10,11} These changes in physiology can impact an older adult's ability to tolerate cancer therapy. The specific vulnerabilities or drug interactions may be more apparent in a clinical trial population enriched for older adults.

2) Disease biology in older adults differs from that in younger adults—Clinical trials focusing on older adults are particularly useful when the biology of that particular cancer is known to be different in older adults. An example is acute myelogenous leukemia, where increasing age is associated with a more aggressive biology that does not respond to standard therapies.¹²⁻¹³ Specifically targeting an older age group could provide insight into the biology of a certain form of disease as it presents in older adults, and thus lead to novel therapeutic options in this setting.

3) Additional or different outcomes are of special interest in the geriatric oncology population—Traditional oncology treatment trials focus on disease-free and overall survival. While these endpoints concern older patients, other endpoints may be just as important to them. A survey of older adults demonstrated that the impact of treatment on physical and cognitive functioning was, in some instances, even more important than curing the disease.¹⁴ Therefore, measuring the impact of therapy on short- and long-term physical function (or maintenance of “active life expectancy”) and cognition should be considered as an integral part of the decision-making process in an older population, and are examples of an endpoint that could be included in a geriatric oncology clinical trial.

4) Adults above a certain age have been underrepresented in clinical trials that theoretically encompass patients of all ages—Developing clinical trials that target older adults may also increase the number of older adults with the disease who enroll in clinical trials. This was demonstrated by a review of 4 randomized clinical trials in breast cancer across a quarter of a century, which demonstrated that only 9% of patients in those clinical trials were older than 65.¹⁵ Developing a trial specifically for older adults immediately increased the number of older adults in randomized trials. For example, CALGB 49907 randomized 634 older adults with breast cancer to either standard chemotherapy (AC [Adriamycin and cyclophosphamide] or CMF [cyclophosphamide, methotrexate, and 5-fluorouracil]) or an oral chemotherapy regimen of single-agent capecitabine.¹⁵

The following challenges were identified in designing a trial for older adults. The first and most basic challenge is that there is no accepted chronological age for inclusion in a geriatric oncology clinical trial. While many geriatric oncology studies focus on patients age ≥ 65 , this is an arbitrary cut-off based on chronological age, which is a poor descriptor of physiologic age in an older adult. However, there are ways to select an appropriate age criteria: 1) Evaluate the age distribution of older adults in existing trials in order to identify where accrual is low, and design trials specifically for the age group that has been underrepresented for that disease type. This approach will fill a gap in research knowledge regarding these older adults, while simultaneously avoiding overlap with other open studies. 2) Identify the age cohort in which the efficacy of therapy or toxicity is different in an older vs younger population. Study design can include modifications in therapeutics or supportive care measures to address each concern.

Measuring Therapeutic Outcomes by Subset Analysis

Clinical trials traditionally include adults of all ages. Subset analyses regarding the efficacy and toxicity of treatment by age in these trials can identify differences in efficacy and toxicity in the older adult population. To date, such analyses have been limited by the low number of older adults enrolled in clinical trials, so it is not known whether the patients who enroll represent the population as a whole. In addition, little about physiologic age is included in trial designs. Performance status is typically captured by KPS or ECOG status. Comorbid conditions or concomitant medications are infrequently captured. Therefore, while the study might identify the fact that older adults are more vulnerable to toxicity with a given therapy, there is little information to help researchers identify which of many factors contribute to the toxicity, other than chronological age. In addition, given the low representation of older adults in clinical trials, investigators may not have a sufficient sample size to identify a difference even if it is present, or if a difference is present, the confidence intervals may be too wide.

Conference investigators discussed ways to increase the value of subset analyses by age. One potential mechanism is to identify at the start of the trial the proportion of patients

needed in order to have an adequate representation of older adults. The statistical design of the trial could specify including a certain proportion of older patients within each age group (ie, proportion age 65-70; proportion age >70). The trial would remain open until each age group cohort completed enrollment. Second, include a baseline assessment of factors other than chronological age that may have an impact on treatment toxicity. This approach would help identify the characteristics of older adults who are “fit,” “vulnerable,” or “frail.”

Identifying Vulnerable vs Fit Older Adults: Incorporating a Geriatric Assessment in Clinical Trials Design

In cancer clinical trials to date, little information is captured about the older adults who enroll, other than chronological age and functional status (via ECOG or KPS). Including a geriatric assessment in cancer clinical trials can help to estimate life expectancy, understand factors other than chronological age that provide an overview of the benefits versus risks of treatment, and develop interventions for those individuals who are most vulnerable. This assessment includes an evaluation of functional status, comorbidity, psychological state, cognitive function, social support, and nutritional status. Each of these factors is an independent predictor of morbidity and/or mortality in older adults.¹⁶

The conference members discussed the feasibility and value of integrating a geriatric assessment as part of the baseline workup of older adults in cancer clinical trials. The assessment would highlight factors other than chronological age that predict cancer treatment morbidity and mortality. In addition, this assessment can pinpoint competing causes of morbidity or mortality that may affect tolerance to cancer treatment. These competing causes of morbidity and mortality could also influence life expectancy (in the absence of cancer), and therefore influence the decision-making process regarding whether someone might derive benefits from adjuvant cancer treatment during the life expectancy remaining.

The goal of a geriatric assessment would also be to identify patients at risk for cancer or cancer treatment-related complications and develop interventions to assist those patients through the treatment course. Including a geriatric assessment at serial time points can help to avoid the longitudinal impact of treatment on functional status, and guide the development of interventions to decrease treatment toxicity and maintain function. One such example is the French trial INOGAD (Nutritional Trial in Geriatric Oncology), which is evaluating the utility of a nutritional intervention in older patients with cancer.

The panel acknowledged that in order for a geriatric assessment to be feasible for incorporation in cancer clinical trials, it must be brief and primarily self-administered. Efforts are being made to identify short geriatric assessment tools. A French trial, ONCODAGE, is evaluating the utility of a comprehensive (longer) geriatric assessment versus shorter screening tools, such as the Vulnerable Elders Survey-13 and a geriatric screen of 8 questions. A primarily self-administered geriatric assessment for inclusion in clinical trials has been pilot tested in the Cancer and Leukemia Group B.¹⁷ The PACE (Pre-Operative Assessment of Cancer in the Elderly) trial has evaluated the utility of a geriatric assessment in patients undergoing surgery.¹⁸

Clinical Trials for Frail or Vulnerable Patients Regardless of Age

The need for standard definitions of “fit,” “vulnerable,” and “frail” patients was described by the panelists as an area of high research priority. One way to characterize eligibility for clinical trials of vulnerable or frail patients would be to include patients: 1) who do not meet standard inclusion criteria for the main clinical trial for patients of all ages; or 2) who are not enrolled because of a doctor's concern regarding standard therapy tolerance. While these

trials will likely accrue a high proportion of older patients, all ages could be eligible. An example of this trial design is the North Central Cancer Group (N0422) trial, a single-arm phase II study evaluating cetuximab in combination with radiation for patients with locally advanced non-small cell lung cancer. This study includes patients age ≥ 65 and those with poor performance status. Other panelists recommended separating patients with a poor performance status from those who are age ≥ 65 , pointing to studies showing that elderly adults who enroll in clinical trials generally derive similar benefits to younger adults. In addition, studies are needed to differentiate patients with a poor performance status from underlying comorbidity rather than the cancer.

The investigators discussed novel phase I therapeutic designs [PIIC (progressive increasing inclusion criteria) trial design] to establish the maximally tolerated dose in patients with functional decline or comorbidity.¹⁹ This design will help to establish how comorbidity and functional status influence the optimal dose in a vulnerable older patient population. The first cohort of patients is functionally independent with few comorbid illnesses. These patients receive the established chemotherapy dose from phase I trials. With each progressive cohort of patients, the inclusion criteria allow the entry of patients with increasing comorbidity and decreasing functional status in order to establish the therapeutically safe dose in these patient populations. This study design is being considered within the Southwest Oncology Group.

Advancing Geriatric Oncology in Cooperative Groups: Recommendations for Future Research

To improve our knowledge of the efficacy and toxicity of cancer therapeutics in older adults, several strategies were suggested. First, identify the age group of older adults who are underrepresented on clinical trials, and develop trials specifically for these patients. Second, develop therapeutic studies for older adults who are not eligible for standard clinical trials (because of comorbidity or functional status), or for patients who are deemed to be at high risk for toxicity from standard therapy (frail or vulnerable). Third, design trials dictating that a certain proportion of older adults are to be included in the trial for subset analyses. Inclusion of a geriatric assessment in therapeutic clinical trials can identify factors other than chronologic age, and identify those older adults who are “vulnerable” (at risk for toxicity) and “fit” (able to tolerate cancer therapy without significant toxicity). These data can be used to target interventions that decrease the risk of toxicity among vulnerable older adults.

While progress has been made in geriatric oncology, conference attendees acknowledged that gaps remain. The committee of cooperative group investigators identified the need for dedicated investigators who focus on geriatric oncology research within the cooperative groups in order to spearhead these efforts. Ultimately, committed leadership is needed to move the field forward. Linking the efforts among cooperative groups will expedite this progress, and this conference was a major first step toward this goal.

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Biography

Dr. Arti Hurria is a geriatrician and oncologist, focusing on care of the older patient with cancer. She completed a geriatric fellowship in the Harvard Geriatric Fellowship Program, followed by a hematology-oncology fellowship at Memorial Sloan-Kettering Cancer Center (MSKCC). She subsequently joined the faculty at MSKCC, where she served as co-

Principal Investigator on the institutional NIH P20 grant “Development of an Aging and Cancer Center at MSKCC.” In the fall of 2006, Dr. Hurria joined the City of Hope as Director of the Cancer and Aging Research Program. Dr. Hurria is a cadre member of the Cancer and Leukemia Group B, Cancer in the Elderly Committee and is a recipient of the Paul Beeson Career Development Award in Aging Research (K23 AG026749-01) and American Society of Clinical Oncology-Association of Specialty Professors-Junior Development Award in Geriatric Oncology. In 2010, she was named Editor-in Chief of the Journal of Geriatric Oncology.

TABLE
International Society of Geriatric Oncology Conference Group Leaders

Participant/Leaders	Affiliation
Riccardo Audisio	National Research Cancer Network, Medical Research Council
Lodovico Balducci	Geriatric Oncology Consortium
Harvey Cohen	Cancer and Leukemia Group B
Jean-Pierre Droz	French Cooperative Group Trials
Martine Extermann	Eastern Cooperative Oncology Group, Southwest Oncology Group
Tamas Fulop	Quebec Society of Geriatrics
Arti Hurria	Cancer and Aging Research Group
Aminah Jatoi	North Central Cancer Treatment Group
Corey Langer	Radiation Therapy Oncology Group & Eastern Cooperative Oncology Group
Jean Latreille	National Cancer Institute of Canada
Silvio Monfardini	GIOGER
Hyman Muss	Cancer and Leukemia Group B
Arash Naeim	TORI
Patricia Olmi	Geriatric Radiation Oncology Group
Pierre Soubeyran	French Group GOELAMS & Bergonie Institute. European Organization for the Research and Treatment of Cancer
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Ulrich Wedding	European Organization for the Research and Treatment of Cancer
Chek-Hooi Wong	Geriatric Oncology Interest Group, The National Cancer Center, Singapore General Hospital
Gilbert Zulian	Swiss Oncology Cooperative Group