JOURNAL OF GERIATRIC ONCOLOGY 6 (2015) 133–140

Available online at www.sciencedirect.com

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Predictors of chemotherapy dose reduction at first cycle in patients age 65 years and older with solid tumors

Ajeet Gajra[a,*], *Heidi D. Klepin*[b], *Tao Feng*[c], *William P. Tew*[d], *Supriya G. Mohile*[e], *Cynthia Owusu*[f], *Cary P. Gross*[g], *Stuart M. Lichtman*[d], *Tanya M. Wildes*[h], *Andrew E. Chapman*[i], *Efrat Dotan*[j], *Vani Katheria*[c], *Laura Zavala*[c], *Chie Akiba*[c], *Arti Hurria*[c,**] *on behalf of the Cancer and Aging Research Group (CARG)*

[a]*Upstate Medical University and VA Medical Center, Syracuse, NY, USA*
[b]*Wake Forest School of Medicine, Winston-Salem, NC, USA*
[c]*City of Hope Comprehensive Cancer Center, Duarte, CA, USA*
[d]*Memorial Sloan-Kettering Cancer Center, New York, NY, USA*
[e]*University of Rochester, Rochester, NY, USA*
[f]*Case Western Reserve University, Cleveland, OH, USA*
[g]*Cancer Outcomes, Public Policy, and Effective Research Center (COPPER), Yale School of Medicine, New Haven, CT, USA*
[h]*Washington University School of Medicine, St Louis, MO, USA*
[i]*Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA*
[j]*Fox Chase Cancer Center, Philadelphia, PA, USA*

ARTICLE INFO

Article history:
Received 16 August 2014
Received in revised form
25 November 2014
Accepted 3 December 2014
Available online 7 February 2015

Keywords:
Elderly
Geriatric oncology
Chemotherapy dose
Geriatric assessment

ABSTRACT

Purpose: Age-based reduction of chemotherapy dose with the first cycle (primary dose reduction, PDR) is not routinely guideline recommended. Few studies, however, have evaluated how frequently PDR is utilized in the treatment of older patients with cancer and which factors may be associated with this decision.

Methods: We conducted a secondary analysis of a multi-institutional prospective cohort study of patients age ≥65 years treated with chemotherapy. The dose and regimen were at the discretion of the treating oncologist. The prevalence of PDR and its association with treatment intent (palliative vs. curative), tumor type, patient characteristics (sociodemographics and geriatric assessment variables), and chemotherapy-associated toxicity were evaluated.

Results: Among 500 patients (mean age 73, range 65–91 years), 179 patients received curative intent chemotherapy and 321 patients received palliative intent chemotherapy, with PDR being more common in the latter sub-group (15% vs. 25%, p = 0.005). Increasing age was independently associated with PDR in both sub-groups. Comorbidity (prior cancer or liver/kidney disease) was independently associated with PDR in the palliative sub-group alone while Karnofsky Performance Status (KPS) was not associated with PDR in either subgroup. There was no significant difference in the rates of grades 3–5 toxicity, dose reductions, or delays with PDR. Patients in the palliative sub-group treated with PDR had higher rates of hospitalization compared to those treated with standard doses.

* *Correspondence to:* A. Gajra, Upstate Medical University, 750 E Adams Street, CWB#2275, Syracuse, NY 13210, USA. Tel.:+1 315 4648286; fax: +1 315 464 8279.
** *Correspondence to:* A. Hurria, City of Hope, 1500 E. Duarte Road, Duarte, CA 91010, USA. Tel.: +1 626 256 4673x64173; fax: +1 626 301 8898.
E-mail addresses: gajraa@upstate.edu (A. Gajra), ahurria@coh.org (A. Hurria).

http://dx.doi.org/10.1016/j.jgo.2014.12.002
1879-4068/Published by Elsevier Ltd.

Conclusion: PDR is more common in the palliative setting, but is also utilized among patients treated with curative intent. Factors associated with PDR include age and comorbid conditions, but not KPS.

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1. Introduction

Several studies have demonstrated that older adults gain as much benefit from chemotherapy as younger patients.[1,2] However, the risk of toxicity associated with chemotherapy increases with age.[3,4] Age-related comorbidity and physiologic changes such as a decline in renal and hepatic function, loss of muscle mass as well as decreased hematopoietic reserve all contribute to a greater incidence of chemotherapy-associated toxicity in older adults.[5–7] Consequently, older adults are less likely to be offered chemotherapy largely due to concerns regarding their ability to tolerate the treatment.[8,9] Chemotherapy dose reductions that ultimately lead to decreased relative dose intensity are also common in older patients and may compromise treatment efficacy.[10–12] The prevalence of a planned dose reduction of chemotherapy at first cycle, designated as primary dose reduction (PDR), and the factors associated with PDR in clinical practice are not well studied.

Current treatment guidelines as issued by the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) do not recommend chemotherapy dose modification with the first cycle based on age.[13] Medical oncologists, however, may use their clinical judgment to reduce the chemotherapy dose preemptively in an effort to avoid toxicity. The factors that may impact such decision-making are not well established. These factors may include patient demographic factors (age, gender, living situation, educational status), disease factors (stage of disease, intent of therapy [curative or palliative], type of cancer), the nature of the chemotherapy regimen, as well as clinical assessment of the patient's performance status and comorbid conditions. However, the relative weight that the oncologist assigns to each of these factors in the decision-making process is not clear. The potential benefit of PDR in reducing toxicity is not known nor is its potential for decline in efficacy. Importantly, the risks and benefits of such a practice may differ by treatment intent (curative versus palliative). Thus, the objectives of the present study were: (i) to evaluate the prevalence of PDR in patients age ≥65 years receiving chemotherapy for cancer with either curative or palliative intent; (ii) to study the association of tumor, treatment, sociodemographic factors, and geriatric assessment variables with PDR stratified by treatment for curative or palliative intent; and (iii) to study the association between PDR and chemotherapy toxicity (grades 3–5 toxicity, chemotherapy dose delay, dose reduction, discontinuation or hospitalization).

2. Methods

This study is a secondary analysis of data from a multi-center, longitudinal study evaluating the utility of a comprehensive geriatric assessment in predicting chemotherapy toxicity among a cohort of older adults with cancer.[14] This study was approved by the Institutional Review Board at all seven participating sites. Patients were eligible for the study if they were age 65 years or older, had a diagnosis of cancer (excluding non-melanoma skin cancers and hematologic malignancies), were scheduled to receive a new chemotherapy regimen recommended by their primary oncologist, were English-speaking, and were able to provide informed consent. Patients receiving concurrent radiation were excluded as were patients receiving biologic agents (e.g. bevacizumab). Patients with metastatic or recurrent disease were designated as receiving chemotherapy with palliative intent. Patients with earlier stage disease (stages I–III), receiving adjuvant, neoadjuvant or consolidation chemotherapy were designated as receiving curative intent chemotherapy.

2.1. Procedures

Patients completed a baseline comprehensive geriatric assessment, which included a standardized evaluation of their comorbidity and social support as well as their functional, nutritional, cognitive, and psychological status.[14] All patients were treated with a chemotherapy regimen and dose as considered appropriate by their treating oncologist. The medical oncologist did not have the results of the geriatric assessment at the time of decision-making regarding chemotherapy regimen and dose. Primary dose reduction (PDR) was defined as a dose of chemotherapy which was less than the dose recommended for a given regimen in current treatment guidelines by the NCCN. Lower than recommended dose of even one of the agents in a multi-agent chemotherapy regimen was defined as a dose reduction. Two oncologists individually reviewed each regimen and the recommended dosing to determine whether the dose reduction had occurred at the first cycle and to quantify the percent dose reduction. For patients receiving multi-agent chemotherapy, dose reduction was calculated as a mean of the percentage reduction for each agent (e.g. for a regimen of doxorubicin and cyclophosphamide, if doxorubicin was reduced by 25% and the cyclophosphamide by 15%, then the mean dose reduction was calculated as 20%). The calculated percent dose reduction was individually confirmed by two oncologists. All patients who received recommended doses of chemotherapy as defined by current treatment guidelines were considered to have received standard dose chemotherapy.

2.2. Measures

We evaluated the association between PDR and the following factors:

1) Patient characteristics (age, sex, ethnicity, race, presence of a living companion, and educational status); 2) Tumor characteristics (tumor type and stage); 3) Treatment characteristics (line of chemotherapy [first line or greater than first line] and single agent or polychemotherapy); 4) Geriatric assessment variables including: (i) Functional status (ability to perform activities of