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

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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

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Disclosures and Conflict of Interest Statements

The authors have no conflicts of interest to disclose.

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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.

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.

Keywords

Elderly; Geriatric oncology; Chemotherapy dose; Geriatric assessment

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 daily living assessed by the subscale of the Medical Outcomes Study [MOS] physical health; instrumental activities of daily living [IADLs] as assessed by the Older Americans Resources and Services [OARS] subscale,[15] Karnofsky Performance Status [KPS] scale [both physician- and patient-rated],[16,17] and history of falls in the 6 months prior to study); (ii) Comorbidity number and type (captured by the OARS subscale)[15]; (iii) Psychological status (assessed by the Hospital Anxiety and Depression Scale [HADS])[18,19]; (iv) Nutritional status (percent unintentional weight loss in the 6 months prior to study and body mass index [BMI]); and (v) Cognitive status (assessed by the Blessed Orientation-Memory-Concentration [BOMC] scale).[20,21]

Toxicity outcomes included: incidence of grades 3–5 toxicity per National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 3.0 (overall, hematologic, non-hematologic toxicity), need for hospital admission, dose delays, or early discontinuation of chemotherapy due to toxicity. For the purpose of this analysis, all toxicity outcomes were counted only once. Chemotherapy duration was calculated from the first day the chemotherapy regimen was initiated to the date the last dose was.

2.3. Statistical Considerations

Descriptive analyses were performed to determine mean, median, standard deviation (SD), ranges for continuous variables, and frequencies for categorical variables. Bivariate analyses were conducted separately in the curative intent and palliative intent chemotherapy groups to assess the association between each of the variables and dose reduction at the first cycle of chemotherapy (PDR [yes or no]) utilizing unconditional logistic regression models. The variables reaching a p-value less than 0.1 in the bivariate analysis were further examined by using multivariable logistic regression models. Interaction was examined by adding an interaction term in a multivariable model. Two-sided tests with a significance level of $p < 0.05$ were used. All statistical analyses were performed using SAS statistical software, version 9.2 (Cary, NC).

3. Results

The mean age of participants (N = 500) was 73 years (SD 6.2; range 65–91) with stage I (5%), II (12%), III (22%), and IV (61%) cancer. The most common tumor types were lung (29%), gastrointestinal (27%), gynecologic (17%), and breast (11%) cancer. Of the 500 patients, 70% received polychemotherapy, 79% received standard doses of chemotherapy, 71% received first line treatment, and 18% received primary prophylaxis with white blood cell growth factors.

Among 500 patients, 179 (36%) and 321 (64%) patients received chemotherapy with curative and palliative intent, respectively. The patient characteristics for the curative and palliative intent groups are listed in Table 1.

PDR was documented in 26/179 (15%) and 81/321 (25%) of patients treated with curative and palliative intent, respectively ($p = 0.005$). The mean percentage of dose reduction for the overall population was 25.1% (range: 7%–67%). The mean percentage of dose reduction was 26.7% for the curative intent subgroup and 24.7% for the palliative intent group.

3.1. Curative Intent Chemotherapy Subgroup

Of the 179 patients with stages I–III cancers treated with curative intent chemotherapy, the mean age was 73 years (range 65–89 years). There was a female predominance (64%) and the following distribution of cancer types: 30% gastrointestinal, 22% breast, 21% gynecologic, and 17% lung cancer (Table 2). In this group, 26 patients (15%) received PDR. In comparison to patients treated with standard dose chemotherapy, patients receiving PDR were older (mean age 78.5 vs. 72.1 years, $p < 0.01$), had a higher prevalence of gynecologic cancers (42% vs. 18%, $p < 0.01$), and a lower prevalence of breast cancers (0% vs. 25%, $p < 0.01$). They were more likely to have osteoporosis (38% vs. 18%, $p = 0.02$) and had a lower mean MD-rated KPS (83 vs. 88, $p = 0.03$). There were no significant differences in the scores of other geriatric assessment variables (Table 2). In multivariable analysis, only older age (odds ratio [OR] 1.19; 95% confidence interval [CI] 1.10–1.28) was independently associated with PDR. Grades 3–5 toxicity was observed in 46% of patients with PDR and 56% receiving standard dose. There were no differences in grades 3–5 hematologic and non-hematologic toxicity, hospitalizations, dose reductions, or delays.

3.2. Palliative Intent Chemotherapy Subgroup

Of the 321 patients treated with palliative intent chemotherapy, 81 patients (25%) received PDR (Table 2). The mean age of the patients was 73 years (range 65–91 years). Cancers included advanced lung cancer (35%), gastrointestinal cancers (25%), gynecologic cancers (15%), and genitourinary cancers (12%). Patients who received PDR were more likely to be older, and have a higher incidence of comorbid conditions (diabetes mellitus, heart disease, liver or kidney disease, depression, history of prior cancers, and stomach disorders). Patients with diagnoses of gastrointestinal or genitourinary cancers were more likely to receive PDR. When GA variables were assessed, a history of one or more falls in the preceding 6 months was associated with PDR as well as cognitive deficit as assessed by the BOMC score. The physician and patient-rated KPS were not associated with PDR (Table 2). A diagnosis of lung cancer was associated with decreased likelihood of PDR. In multivariable analysis, factors independently associated ($p < 0.05$) with PDR include: older age (OR 1.10; 95% CI 1.05–1.15), liver/kidney disorders (OR 9.4; 95% CI 3.2–27.8), prior cancer (OR 3.3; 95% CI 1.7–6.2), and a diagnosis of lung cancer (OR 0.51; 95% CI 0.27–0.95) (Table 3). Grades 3–5 toxicity occurred in 50% of patients with PDR and 54% of patients receiving standard dose chemotherapy. In the palliative intent chemotherapy group, patients receiving PDR had a higher incidence of hospitalization (30% vs. 19%, $p = 0.03$). There was no significant difference between PDR and standard dose with respect to types of toxicity reported

(hematologic, non-hematologic), dose delays, or early chemotherapy discontinuation (Table 4).

4. Discussion

In this cohort of older adults with cancer, chemotherapy dose reduction with the first cycle was common, irrespective of the goal of therapy. One in six patients treated with curative intent received PDR as did one in four patients treated with palliative intent chemotherapy. Since the treating oncologists did not have access to the results of the geriatric assessment, their decision to reduce chemotherapy dose was based on their clinical assessments. Age was the only factor independently associated with PDR in both the curative and palliative intent groups. In the latter group, comorbid conditions were also associated with the decision to reduce chemotherapy dose for the first cycle. Impairments detected with geriatric assessment measures were not independently associated with PDR in this analysis. This suggests that commonly captured clinical parameters, like age and comorbidity, are typically used in clinical practice in determining chemotherapy dose. Other factors like functional status, social support, nutritional status, and cognitive function may not be utilized routinely in this process. It has been reported that even when the results of the GA are made available to clinicians, they are not always utilized in decision-making which further points to a need for greater education regarding the potential value of a GA.[22]

The relevance of chemotherapy dose may be greater when administered with curative intent. Dose attenuation may lead to increased risk of relapse and worse survival. Evidence suggests that older adults are undertreated for cancer, which may contribute to age-related disparities in cancer-specific outcomes and survival.[23] Our findings are consistent with others that have found a clear association between older age and chemotherapy dose reduction. In a retrospective study of patients with early stage breast cancer, factors independently associated with PDR (defined as planned dose reduction of >10% at first cycle) included age ≥65 years, high body surface area, and renal disease.[12] In a prospective study of patients with stages I–III breast cancer, treated with adjuvant chemotherapy, PDR (defined as planned dose reductions of >15% with first cycle) was more common among patients ≥65 years compared to younger patients (17% vs. 12%, $p = 0.02$). This study evaluated the impact of dose on severe and febrile neutropenia, which were not different between the two groups.[24] Another prospective study included 363 patients with potentially curable cancer, one-third (33%) of patients received PDR (defined in this study as a planned dose reduction of >15% at cycle 1). ECOG performance status, KPS, and comorbidity (Charlson comorbidity index) were not associated with PDR.[25] Furthermore, similar to the findings in our study, KPS was not independently associated with primary dose reduction. Our study is unique in that it evaluates the association of PDR with hematologic and non-hematologic toxicity as well as other toxicity related end-points, like treatment delays, dose reductions, and hospitalizations, in a variety of cancer types. We did not find any significant difference in grades 3–5 toxicity between patients who received PDR or standard dose chemotherapy in patients treated with curative intent chemotherapy.

The availability and use of a validated tool to better risk stratify older patients could obviate the age bias that may exist among the treating oncologists, thereby avoiding dose reductions in those at lower risk of toxicity so the curative potential of therapy is not compromised.

Few studies have focused on PDR in the palliative setting. We found a strong relationship between increased age and PDR, but also identified comorbid conditions including history of prior cancer or liver/kidney disease in patients treated with palliative intent. Surprisingly, functional status as measured by physician rated KPS, was not associated with PDR. There was no difference in chemotherapy toxicity with PDR except that rates of hospitalization were higher in patients who received PDR suggesting that these patients remain vulnerable despite the planned dose reduction. If PDR serves as a proxy for the physician's concern for the patient to tolerate a standard dose, then this finding might suggest that the oncologist's clinical judgment is successful at identifying vulnerable patients. Thus PDR may be appropriate in some older adults but it is vital to consistently identify the patients who may benefit from such a maneuver. Performance status, long viewed as such a quick measure in the clinic setting is likely an inadequate predictor of chemotherapy toxicity in the older adult with cancer.

Chemotherapy toxicity was high irrespective of the dose used with more than half of older adults experiencing grades 3–5 toxicity, as noted in other studies as well.[25] Strategies to risk stratify patients prior to chemotherapy are important. Many such models are under development.[14,26,27] If reliably identified, then strategies to minimize toxicity could be utilized to prospectively determine whether modifying chemotherapy doses in groups of patients with specified cancer and stage influences the risk of chemotherapy toxicity and efficacy. Such trials in the past have not addressed the question of chemotherapy dosing.[28,29] Randomized studies in patients with advanced cancer are needed to understand the risks and benefits of PDR. Use of new trial designs, such as are utilized in the FOCUS2 trial, may elucidate the risks and benefits of PDR for older patients deemed to be unfit for standard doses of chemotherapy. The patients in this trial received 80% of standard doses to start and were subsequently escalated to full dose at 6 weeks per the treating physician's discretion.[30]

We conducted an exploratory analysis using the Cancer and Aging Research Group (CARG) toxicity tool where we studied the risk of toxicity in patients who were treated with PDR. The model appeared to discriminate for risk of toxicity for the entire group as well as for standard dose and PDR groups (Table 5). About 33% (32/104) of patients in the PDR group were at low risk of toxicity based on this model suggesting that a third of older patients that receive a primary dose reduction may be at low risk for chemotherapy associated toxicity.

Limitations of the current study include that it is a secondary analysis of a prospective observational study. The study included patients with several tumor types. The reasons for primary dose reductions were not captured. For patients treated with second or subsequent line of chemotherapy, toxicity to first line therapy may have played a role in the decision to reduce chemotherapy dose, but that data was not available for review. Furthermore, the association between primary dose reduction and its impact on treatment efficacy cannot be answered from this dataset. Despite these limitations, this study has significant strengths. It

provides information regarding the frequency of primary dose reduction among patients treated at multiple centers across the US, captures patterns of chemotherapy dosing, and identifies the characteristics of those patients who were most likely to receive a PDR.

The frequency of PDR of chemotherapy in older adults with cancer provides a rationale for prospectively studying whether modifying dosing with the first cycle influences either toxicity or efficacy in this growing group of older adults with cancer. Evidence based guidelines to guide the dosing of chemotherapy in this population are urgently needed. Such information is likely best obtained in trials specific to the older adult which should have broad inclusion and minimal, if any, exclusion criteria for participation.

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Table 1

Patient characteristics comparison between the palliative intent group and curative intent group (N = 500).

Variable	Curative intent group (n = 179) [a]	Palliative intent group (n = 321)[b]	p-Value
Age, years			
Mean (range)	73.0 (65–89)	73.2 (65–91)	0.82
SD	6.1	6.3	
	No. (%)	No. (%)	
Race			
White	144 (80.4)	282 (87.9)	0.05
Black	23 (12.9)	19 (5.9)	
Asian	9 (5.0)	17 (5.3)	
Other	3 (1.7)	3 (0.9)	
Gender			
Male	64 (35.8)	155 (48.3)	0.007
Female	115 (64.2)	166 (51.7)	
BMI			
<25	88 (49)	165 (51.7)	0.58
≥25	91 (51)	154 (48.3)	
Missing		2	
Cancer type			
Breast	39 (21.8)	18 (5.6)	<0.001
Lung	31 (17.3)	112 (34.9)	
GI	54 (30.2)	81 (25.2)	
GYN	38 (21.2)	49 (15.3)	
GU	11 (6.2)	39 (12.2)	
Other	6 (3.3)	22 (6.8)	
Education			
Less than high school	6 (3.4)	12 (3.8)	0.86
High school graduate	60 (33.5)	115 (35.9)	
Associate/bachelor’s degree	77 (43.0)	125 (39.0)	
Advanced degree Missing	36 (20.1)	68 (21.3)	
Marital status			
Married	109 (60.9)	197 (61.4)	0.70
Widowed	43 (24.0)	70 (21.8)	
Single	7 (3.9)	9 (2.8)	
Separated, divorced	20 (11.2)	45 (14.0)	
Employment status			
Full or part time	25 (14.0)	58 (18.1)	0.46
Retired, homemaker, unemployed	147 (82.1)	248 (77.5)	
Disabled, medical leave	7 (3.9)	14 (4.4)	
Missing		1	
Standard dose			

Variable	Curative intent group (n = 179) [a]	Palliative intent group (n = 321)[b]	p-Value
Yes	153 (85.5)	240 (74.8)	0.005
No	26 (14.5)	81 (25.2)	
First line of chemotherapy			
Yes	165 (92.2)	190 (59.2)	<0.001
No	14 (7.8)	131 (40.8)	
No. of chemotherapy drugs			
Mono-chemotherapy	28 (15.6)	121 (37.7)	<0.001
Poly-chemotherapy	151 (84.4)	200 (62.3)	
Duration, days			
Mean (range)	92.8 (1–491)	94.0 (1–598)	0.854
SD	65.0	81.0	

Abbreviations: SD, standard deviation; BMI, body mass index; GI, gastrointestinal; GYN, gynecologic; GU, genitourinary.

[a] Includes stages I–III disease, except IIIb lung cancer

[b] Includes stage IV disease and stage IIIb lung cancer.

Table 2

Association between demographic/clinical factors and chemotherapy doses for the palliative intent group (N = 321) and curative intent group (N = 179).

Variable	Curative intent group			Palliative intent group		
	Primary dose reduction (n = 26)	Standard dose (n = 153)	p-Value	Primary dose reduction (n = 81)	Standard dose (n = 240)	p-Value
Age, years						
Mean (range)	78.5 (66–89)	72.1 (65–87)	<0.01	75.8 (65–91)	72.3 (65–89)	<0.001
SD	6.6	5.5		6.8	5.8	
	No. (%)	No. (%)		No. (%)	No. (%)	
Gender						
Male	9 (35)	55 (36)	0.90	39 (48)	116 (48)	0.98
Female	17 (65)	98 (64)		42 (52)	124 (52)	
Race						
White	24 (92)	120 (78)	0.10	74 (91)	208 (87)	0.26
Non-White	2 (8)	33 (22)		7 (9)	32 (13)	
BMI						
<25	19 (73)	69 (45)	0.008	45 (56)	120 (50)	0.42
≥25	7 (27)	84 (55)		36 (44)	118 (50)	
Missing						
Marital status						
Married	14 (54)	95 (62)	0.43	46 (57)	151 (63)	0.33
Widowed	10 (38)	33 (22)	0.06	22 (27)	48 (20)	0.18
Household composition						
Living alone	9 (35)	30 (20)	0.10	18 (23)	49 (20)	0.69
Other	17 (65)	120 (80)		62 (77)	191 (80)	
Missing		3		1		
Cancer type						
Breast	0 (0)	39 (25)	<0.01	4 (5)	14 (6)	0.99
GI	9 (35)	45 (29)	0.59	23 (28)	58 (24)	0.45
GU	2 (8)	9 (6)	0.66	13 (16)	26 (11)	0.21
GYN	11 (42)	27 (18)	<0.01	15 (19)	34 (14)	0.35
Lung	4 (15)	27 (18)	0.99	21 (26)	91 (38)	0.05

Variable	Curative intent group			Palliative intent group		
	Primary dose reduction (n = 26)	Standard dose (n = 153)	p-Value	Primary dose reduction (n = 81)	Standard dose (n = 240)	p-Value
Comorbid conditions						
Arthritis	14 (54)	74 (48)	0.61	34 (42)	107 (45)	0.68
Circulatory problem	5 (19)	16 (10)	0.20	15 (19)	40 (17)	0.70
Depression	4 (15)	17 (11)	0.53	18 (22)	28 (12)	0.02
Diabetes mellitus	3 (12)	28 (18)	0.40	10 (12)	40 (17)	0.35
Emphysema	3 (12)	10 (7)	0.36	10 (12)	31 (13)	0.89
Glaucoma	1 (4)	19 (12)	0.32	12 (15)	17 (7)	0.04
Hypertension	12 (46)	83 (54)	0.44	45 (56)	119 (50)	0.35
Heart disease	6 (23)	25 (16)	0.40	26 (32)	44 (18)	0.01
Liver/kidney disease	1 (4)	2 (1)	0.38	13 (16)	6 (3)	<0.01
Other cancers	6 (23)	23 (15)	0.30	28 (35)	35 (15)	<0.01
Osteoporosis	10 (38)	27 (18)	0.02	13 (16)	33 (14)	0.61
Stomach disorders	3 (12)	26 (17)	0.77	24 (30)	42 (18)	0.02
Stroke	1 (4)	6 (4)	0.99	5 (6)	5 (2)	0.07
	Mean (range)	Mean (range)		Mean (range)	Mean (range)	
SD	21.0	23.7		26.1	26.5	
IADL	13.2 (4–14)	13.3 (8–14)	0.65	12.7 (7–14)	12.7 (5–14)	0.84
SD	2.0	1.3		1.8	2.0	
MD KPS	83.2 (50–100)	88.2 (60–100)	0.03	82.8 (60–100)	83.4 (50–100)	0.65
SD	12.5	9.7		11.7	11.7	
Self-rated KPS	90 (60–100)	89.6 (50–100)	0.87	81.3 (40–100)	83.9 (50–100)	0.14
SD	11.5	12.3		14.4	13.7	
Falls	0.3 (0–3)	0.3 (0–3)	0.64	0.6 (0–6)	0.2 (0–4)	0.02
SD	0.8	0.7		1.2	0.6	
Social activity	57.6 (25–94)	61.0 (0–100)	0.44	51.2 (0–100)	54.6 (0–100)	0.31
SD	17.2	21.3		27.2	22.2	
Social support	80.3 (41–100)	84.7 (0–100)	0.34	84.4 (10–100)	85.6 (0–100)	0.65
SD	18.1	22.1		21.0	21.4	
BOMC (≥11) N (%)				2 (3)	20 (8)	0.08

Abbreviations: SD, standard deviation; BMI, body mass index; GI, gastrointestinal; GYN, gynecologic; GU, genitourinary; MOS, Medical Outcomes Study; IADL, instrumental activities of daily living; KPS, Karnofsky Performance Status; BOMC, Blessed Orientation-Memory-Concentration.

Table 3

Predictors for PDR in the palliative intent chemotherapy group (multivariable analysis).

Variables	OR	95% CI	p-Value
Age	1.10	1.05–1.15	<0.001
Lung cancer vs. other	0.51	0.27–0.95	0.035
Liver/kidney disease vs. other	9.43	3.20–27.79	<0.001
Other cancers	3.26	1.71–6.22	<0.001
Cognitive impairment (BOMC)	0.41	0.08–2.10	0.29

Table 4

Distribution of adverse events for the PDR group and standard dose group.

Adverse events	Primary dose reduction	Standard dose	P value
	No. (%)	No. (%)	
Grades 3–5 toxicity[a]	54 (50.5)	212 (53.9)	0.52
Grade 3 toxicity	52 (48.6)	199 (50.6)	0.71
Grade 4 toxicity	8 (7.5)	51 (13.0)	0.10
Grade 5 toxicity	2 (1.9)	7 (1.8)	0.95
Heme toxicity	29 (27.1)	102 (26.0)	0.81
Non-heme toxicity	43 (40.2)	174 (44.3)	0.45
Hospitalization	29 (27.1)	86 (21.9)	0.26
Dose reduction	28 (26.7)	125 (31.8)	0.26
Dose delay	31 (29.0)	124 (31.6)	0.61
Discontinuation of chemo	23 (21.5)	83 (21.1)	0.93

[a]The total n for combined appears lower than the sum of grades 3, 4, and 5 toxicity since only worst toxicity was included in the sum.

Table 5

Exploratory analysis of distribution of patients with varying risks of grades 3–5 chemotherapy toxicity.

Model-based toxicity risk ↓	Full cohort, N = 464[a]			Standard dose, N = 360			Primary dose reduction, N = 104		
	N	%	p-Value	N	%	p-Value	N	%	p-Value
Low	39/128	30	<0.0001	29/96	30	<0.0001	10/32	31	0.0012
Medium	118/227	52		96/182	53		22/45	49	
High	90/109	83		69/82	84		21/27	78	

[a]Sample size reflects patients who had complete data for the 11 variables comprising the CARG toxicity score.