Journal of Geriatric Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

Frequency and impact of grade three or four toxicities of novel agents on outcomes of older patients with chronic lymphocytic leukemia and non-Hodgkin lymphoma (alliance A151611)☆

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ARTICLE INFO

Article history:
Received 3 November 2017
Received in revised form 5 February 2018
Accepted 30 March 2018
Available online xxxx

Keywords:
Non-Hodgkin lymphoma
Chronic lymphocytic leukemia
Toxicity
Older patients

ABSTRACT

Objective: Older patients with cancer suffer from chemotherapy-related toxicities more frequently than younger patients. As novel agents are being used more commonly in chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL), toxicities of these agents in older patients have not been well studied. Further, impact of these toxicities on outcomes in the elderly is unknown. This study aimed to answer both questions.
Patients and Methods: We reviewed 14 Alliance for Clinical Trials in Oncology trials that enrolled CLL and/or NHL patients between 2004–2014. Toxicity was assessed per the NCI-CTCAE (version 3–5). Probabilities of experiencing grade three or four hematologic and non-hematologic toxicities were modeled as a function of clinical and disease-related factors using logistic regression.
Results: 1199 patients (409 age ≥ 65; 790 age < 65) were analyzed; 438 received only biologic therapy (145 age ≥ 65; 293 age < 65), and 761 received biologic + chemotherapy (264 age ≥ 65; 497 age < 65). The odds of grade three or four hematologic [odds ratio (OR) 1.70; $p = 0.009$: 95% CI (1.57–1.84)] and non-hematologic toxicities [OR 1.47; $p = 0.022$; 95% CI (1.39–1.55)] were increased in older patients with CLL, as well as odds of grade three or four non-hematologic toxicities [OR 1.89; $p = 0.017$; 95% CI (1.64–2.17)] in older patients with NHL. Grade three or four hematologic toxicities were associated with inferior OS and PFS in older patients with NHL [HR 3.14; $p = 0.006$; 95% CI (2.25–4.39) for OS and 3.06; $p = 0.011$; 95% CI (2.10–4.45) for PFS], though not in CLL. A prognostic model predicting grade three or four toxicities was also developed.
Conclusions: CLL and NHL patients ≥ 65 year encounter more toxicities than younger patients even when treated with novel biologic agents. Development of grade three or four hematologic toxicities lead to inferior PFS and OS in NHL but not in CLL.

1. Introduction

Advanced age is associated with increased incidence of chronic lymphocytic leukemia (CLL) and Non-Hodgkin Lymphoma (NHL), with a median age of diagnosis >65 for both [1]. Chemoimmunotherapy has markedly improved outcomes in patients with CLL/NHL, but despite

☆ Presented in part as an oral session at the Annual American Society of Hematology meeting in December 2016 San Diego, CA.

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https://doi.org/10.1016/j.jgo.2018.03.018
1879-4068/

advances, older age has consistently been shown to be associated with poorer outcomes [2,3]. Older patients usually present with different characteristics, including increased cardiovascular and pulmonary comorbidities, and have worse outcomes than their younger counterparts, possibly due to an inability to tolerate cytotoxic therapy, potential under-treatment, and sequelae of aging itself [4–9].

Models have been constructed to identify the risk of chemotherapy toxicity in older patients with cancer. A model employing geriatric assessment variables, laboratory test values, histologies, and treatment characteristics was developed to predict grade three through five toxicities in patients age 65 and older treated with chemotherapy [10]. However, <6% of patients in this model had hematologic malignancies, underscoring the need for predictive models designed specifically for hematologic cancers. The increasing use of novel agents in CLL and NHL provides different toxicities than what is encountered with traditional chemotherapy and need to be studied. The frequency of these toxicities and how they might influence outcomes have not been adequately studied.

We aimed to better understand the frequency of toxicities in older patients treated with novel agents for CLL and NHL. Moreover, we sought to assess the degree to which toxicity affected overall survival (OS) and progression free survival (PFS) among these patients.

2. Patients and Methods

We utilized data collected by the Alliance for Clinical Trials in Oncology to: 1) compare the frequency of toxicities between older (≥65 years old) and younger (<65 years old) patients, 2) model OS and PFS of patients as a function of toxicity of treatment with novel drugs including biologic combinations, monoclonal antibodies, cell cycle inhibitors, chemoimmunotherapy, and immunomodulators, and 3) identify characteristics which may help determine a patient's risk of experiencing toxicities when receiving novel therapies. Age ≥ 65 was chosen as a cut-off based on traditional definitions of older adults, under-representation in clinical trials [11–12], and a demonstrated higher risk of chemotherapy toxicity [10,13].

2.1. Between-age Comparisons of Impact of Treatment on Toxicity

The probability of experiencing grade three or four hematologic and non-hematologic toxicities was modeled separately as a function of age (≥65 years vs. <65), specific study, time on study, treatment (novel agents only vs. novel agents plus chemotherapy), gender, race, lactate dehydrogenase (LDH), performance status (PS), stage, and an age-by-treatment interaction using logistic regression. These analyses were conducted separately for patients with CLL and NHL.

2.2. Analysis of Relationship Between Toxicity and OS/PFS in Older Patients

To assess the extent to which these toxicities were associated with OS and PFS in patients ≥65 years, several landmark analyses were performed. Specifically, patients ≥65 years were classified based on whether they experienced at least one grade three or four hematologic toxicity before the landmark time, which we defined as three months after beginning treatment. For patients who were still on study after the landmark time, OS was redefined as the time from the landmark (three months) to death. PFS was redefined in a similar fashion. These endpoints were then modeled separately as a function of the landmark-based toxicity status, time on study, treatment, gender, race, LDH, PS, and stage using Cox proportional hazards models. In addition, as age effects were likely to vary across studies, a random, study-specific intercept and a random study-specific age effect were included in these models. The landmark time of three months was chosen to reflect the initial time of imaging/disease reassessment and to account for lead-time bias and under-reporting of toxicities because of early treatment discontinuation due to underlying disease or other factors.

2.3. Exploratory Classification and Regression Tree (CART) Analyses

Classification and regression trees were used to identify patient characteristics that might be associated with the probability of experiencing toxicities [14]. These models work by recursively partitioning the data into subgroups (defined using patient characteristics), across which the average response (i.e., the probability of experiencing a grade three or four toxicity) differs. More specifically, a brief overview of the CART algorithm we used is as follows:

1. Beginning with the entire data set, consider all possible partitions of the data based on a single covariate, e.g. $X > 5$ vs $X \leq 5$. For each such partition (i.e. for each observed value of each covariate), calculate the value of the splitting criterion, denoted **s.**
2. In our case, **s** is a measure of the predictive accuracy, with smaller values indicating "better" prediction, so we next select the partition that gives the smallest value of **s**, this results in the data being divided into two parts, referred to as "child" nodes.
3. Within each child node, repeat steps 1 and 2.
4. Continue in this fashion until pre-defined stopping criteria are met. In our case, we set the maximum depth to be two (meaning the

Table 1
Baseline characteristics by age group for patients with CLL.

	<65 (N = 477)	≥ 65 (N = 259)	Total (N = 736)	*p* value
Gender				0.755[a]
Unknown	1 (0.2%)	0 (0.0%)	1 (0.1%)	
Male	324 (67.9%)	175 (67.6%)	499 (67.8%)	
Female	152 (31.9%)	84 (32.4%)	236 (32.1%)	
Race				0.390[a]
Unknown	8 (1.7%)	4 (1.5%)	12 (1.6%)	
White	422 (88.5%)	235 (90.7%)	657 (89.3%)	
Black or African American	41 (8.6%)	16 (6.2%)	57 (7.7%)	
Asian	1 (0.2%)	1 (0.4%)	2 (0.3%)	
American Indian or Alaska Native	0 (0.0%)	2 (0.8%)	2 (0.3%)	
Not reported	1 (0.2%)	0 (0.0%)	1 (0.1%)	
More than one race	4 (0.8%)	1 (0.4%)	5 (0.7%)	
Ethnicity				0.122
Hispanic or Latino	1 (0.2%)	4 (1.5%)	5 (0.7%)	
Non-Hispanic	459 (96.2%)	245 (94.6%)	704 (95.7%)	
Unknown	1 (0.2%)	2 (0.8%)	3 (0.4%)	
Not reported	16 (3.4%)	8 (3.1%)	24 (3.3%)	
Performance score				0.036[a]
Missing	1 (0.2%)	1 (0.4%)	2 (0.3%)	
0	284 (59.6%)	131 (50.6%)	415 (56.4%)	
1	179 (37.5%)	114 (44.0%)	293 (39.8%)	
2	13 (2.7%)	13 (5.0%)	26 (3.5%)	
LDH				0.460[b]
N	468	258	726	
Mean (SD)	306.4 (228.9)	306.0 (229.6)	306.3 (229.0)	
Median	223.0	232.5	225.5	
Q1, Q3	169.5, 371.5	175.0, 333.0	171.0, 349.0	
Range	(6.0–1820.0)	(93.0–1877.0)	(6.0–1877.0)	
Stage				<0.001[a]
Missing	9 (1.9%)	6 (2.3%)	15 (2.0%)	
Stage 0	27 (5.7%)	21 (8.1%)	48 (6.5%)	
Stage 1/2	297 (62.3%)	111 (42.9%)	408 (55.4%)	
Stage 3/4	144 (30.2%)	121 (46.7%)	265 (36.0%)	

CLL-chronic lymphocytic leukemia.
PS-performance status.
LDH-lactate dehydrogenase.
SD-standard deviation.
Q-quartile.
[a] Chi-square.
[b] Kruskal Wallis.

Please cite this article as: Tallarico M, et al, Frequency and impact of grade three or four toxicities of novel agents on outcomes of older patients with chronic lymphocytic leuk..., J Geriatr Oncol (2018), https://doi.org/10.1016/j.jgo.2018.03.018