Gynecologic Oncology 149 (2018) 28–32

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Consideration of older patients for enrollment in phase 1 clinical trials: Exploring treatment related toxicities and outcomes

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HIGHLIGHTS

- Older patients did not experience increased toxicity on phase 1 clinical trials.
- Patients ≥70 years old had a clinical benefit rate of 63% on phase 1 clinical trials.
- Strategies to increase enrollment of older patients on clinical trials is imperative.

ARTICLE INFO

Article history:
Received 18 August 2017
Received in revised form 17 November 2017
Accepted 17 November 2017

Keywords:
Clinical trials
Gynecologic malignancies
Elderly

ABSTRACT

Objectives. Age imposes a disparity in the treatment of and outcomes with gynecologic cancer. Older patients are underrepresented in primary treatment trials, but little is known about their ability to withstand trial-based treatment for recurrent or refractory disease. This study sought to examine treatment-related toxicities and outcomes of older versus younger patients participating in phase 1 clinical trials.

Methods. A retrospective analysis of patients enrolled in phase 1 clinical trials for gynecologic malignancies from 2010 to 2016 was performed. Demographic and clinic-pathologic data was abstracted. Toxicities were defined as either grade III or IV by CTCAE criteria. Best response was calculated using RECIST criteria. Associations between categorical variables were determined using Fisher's exact test and continuous variables using Wilcoxon rank sum test. Survival was estimated using the Kaplan-Meier method.

Results. 237 patients were included with 22% ($n = 51$) comprising the older cohort (≥70 years). The vast majority (98%) were treated for recurrent disease. Older patients incurred similar grade III/IV hematologic (21% vs 16%, $p = 0.38$) and non-hematologic toxicities (26% vs 29%, $p = 0.64$). Older patients discontinued treatment due to toxicity only 8% of the time. Median survival was 13.0 and 10.3 months in the <70 and ≥70 groups, respectively ($p = 0.35$). 63% of patients ≥70 achieved clinical benefit.

Conclusions. Although historically older patients have not been routinely considered for enrollment in phase 1 trials, our data demonstrates similar toxicity profiles to that of younger patients and 63% clinical benefit rate. Thus, with careful selection, patients ≥70 should be considered when facing recurrent or refractory gynecologic cancer.

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1. Introduction

Age remains a challenging disparity in the treatment of patients with gynecologic malignancies. It has been well established that age negatively affects a patient's survival. Data from EUROCARE II, a retrospective compilation of European registries, clearly demonstrates this negative relationship in ovarian, cervix and uterine corpus cancers. For example, the one year overall survival rate for ovarian cancer decreases from 57% in those age 65–69 to 25% in those >85 years old [1]. The exact cause of this disparity is unknown; however, it is likely multifactorial with factors both intrinsic to the aging process as well as tumor biology playing a role. For example, it has been cited that older patients with ovarian cancer present with a later stage [2,3], have a higher tumor grade at diagnosis [4], and have more chemo-resistant tumors [5]. Similarly, in endometrial cancer, older patients with early stage who receive standard of care treatments fare worse, suggesting a more aggressive tumor biology [6]. Patients with increasing medical comorbidities and concomitant medications (both of which increase with age) often suffer from

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https://doi.org/10.1016/j.ygyno.2017.11.021
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worse treatment-related toxicities and treatment delays that may impact survival [7,8].

While many of these factors are outside the clinician's control, there is data suggesting that physicians harbor an inherent bias in how they treat their older patients. For example, older patients are less likely to have initial surgical management for ovarian cancer, receive standard chemotherapeutics, and to complete a recommended chemotherapy course [9–12]. Endometrial cancer patients demonstrate a similar decrease in prescribed treatment for advanced disease, including a decrease in the rate of standard surgical management as well as adjuvant chemotherapy or radiation treatment [13].

Similarly, older patients are less likely to be enrolled in clinical trials. Currently the definition of an "older" patient is not consistent in the literature. This is likely to be a fluid definition as life expectancy continues to change. For many studies, the definition of "older" ranges from 65 to 75 years old. While patients over the age of 70 comprise nearly 50% of cancer patients, historically they only represent only 13% of patients on clinical trials [14]. In NCI sponsored trials for gynecologic malignancies, younger patients continue to be over-represented with the greatest disparities seen in ovarian cancer [15]. While, this disparity is present across many trials, there is limited data on enrollment of older patients in Phase 1 clinical trials.

Phase 1 clinical trials serve as a bridge from bench to bedside and are often the first in human trials. The primary objectives of phase 1 clinical trials are safety, tolerability, and maximum tolerated dose. In addition to first in human trials, phase 1 trial design is often utilized to examine other clinical questions such as novel combinations of already approved mediations, new dosing and formulations, or interactions with other food and medications. Currently, the majority of phase 1 trials in gynecologic malignancies are novel targeted agents. This shift away from traditional cytotoxics as well as new FDA accelerated approval tracks has led to newer dosing designs, utilization of biomarkers for patient selection, and tumor specific expansion cohorts to look at efficacy [16].

Given the importance of phase 1 clinical trials on shaping future trial design, it is of utmost importance that these trials represent an inclusive cohort of patients with gynecologic malignancies. To our knowledge, there is no data on how older patients perform in phase 1 clinical trials for gynecologic malignancies. Therefore, our primary objective was to examine the toxicities and treatment outcomes in older patients with advanced gynecologic malignancies enrolled in phase 1 clinical trials at the University of Oklahoma.

2. Methods

This is an IRB-approved retrospective cohort study (IRB #7150). All the Phase 1 trials were conducted at a single institution, The University of Oklahoma Health Sciences Center, Stephenson Cancer Center. Phase 1 trials included first in human dose escalation studies, expansion cohorts, as well as studies looking at novel combinations or new formulations (Phase 1b).

All trial participants from 2010 to 2016 with gynecologic malignancies were included. A retrospective chart review was performed, and demographic, oncologic, and treatment variables were collected. Medical comorbidities collected included hypertension, diabetes, chronic obstructive pulmonary disease (COPD)/lung disease, and coronary artery disease (CAD). Albumin was collected at the time of trial enrollment, and creatinine clearance was calculated from the creatinine, weight and age at the time of enrollment using the Cockcroft-Gault equation. Older patients were defined as those ≥70 years old at the time of original diagnosis. For those patients who enrolled on more than one phase 1 clinical trial, their initial trial data was used for analysis of their demographics, toxicity, response rate, and survival. However, additional analysis was performed for each individual trial for toxicity data.

Toxicity data was collected using Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Grade III and IV toxicities that were attributable to treatment were collected. These were divided into hematologic and non-hematologic. Best response was calculated using RECIST v1.1 criteria for patients who were evaluable for response on restaging scans performed according to the individual protocol. A complete response (CR) was defined as no measurable disease, a partial response (PR) was defined as ≥30% decrease in the sum of the longest diameter of target lesions, and progressive disease (PD) as ≥20% increase in the sum of the longest diameter of target disease. Stable disease (SD) was defined as change that did not meet the above criteria. The sum of the CR, PR or SD defined the clinical benefit rate.

Descriptive statistics for baseline demographics, treatment variables and toxicities were calculated per patient. Categorical variables were compared between patients <70 and ≥70 years using chi-square analysis or Fisher's exact test and continuous variables were compared using Wilcoxon rank-sum test. Kaplan-Meier methods were used to calculate survival curves (from diagnosis and Phase I treatment) for those patients <70 and ≥70 years. The curves were compared using the log-rank test. Descriptive statistics were calculated for all trials for treatment, toxicity, and response variables. An alpha of 0.05 was used. SAS version 9.4 was used for all analyses.

3. Results

Demographics: A total of 386 charts were available for review for a total of 237 unique patients who were enrolled on phase 1 clinical trials from 2010 to 2016. Ninety-one (38%) of these patients enrolled on more than one trial. Demographic information is summarized in Table 1. The older cohort was defined as patients ≥70 years old and consisted of 51 patients (22%) with a median age of 74. One hundred and eighty-eight patients (78%) were <70 years with a median age of 57. A total of 181 (37%) patients <70 years old and 26 (26%) patients ≥70 years old screen failed for phase 1 trials during this time. There was no significant difference in the number or type of medical comorbidities between the two cohorts. Interestingly, 42% and 31% respectively had no significant medical comorbidities, and only 16% and 20% had >1 significant medical comorbidity. Albumin at time of enrollment was not significantly different. The older cohort had lower median creatinine clearance, as expected with increasing age.

Disease site differed between the two cohorts ($p = 0.03$). Most patients had a diagnosis of ovarian cancer (65%); this was not different between the two cohorts (65% and 67% respectively). However, the difference was seen in uterine, cervix, and vaginal cancers. Younger patients had a higher proportion of cervix/vaginal cancer (11% versus 0% for cervix; 2% versus 0% for vaginal). Older patients had a higher proportion of uterine cancer (20% versus 31%). Many of these patients were heavily pretreated, with a median of 2 previous treatment regimens (range, 0–14).

Table 1
Baseline demographics.

Characteristic	Age < 70 years	Age ≥ 70 years	*P* value
Age, median (range)	57 (22–60)	74 (70–86)	
Medical Comorbidities (%)			0.42
None	42	31	
Hypertension	38	47	
Diabetes	2	0	
COPD/Lung Disease	1	0	
CAD	1	2	
Multiple	16	20	
Albumin, median	3.7	3.7	0.99
Creatinine clearance, median	78	50	<0.0001
Disease site, (%)			0.03
Ovary	65	67	
Uterine	20	31	
Cervix	11	0	
Vulva	3	2	
Vagina	2	0	
Prior treatment number, median (range)	2.5 (0–14)	2 (0–8)	0.34

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