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Clinical outcome and prognostic markers for patients with gynecologic malignancies in phase 1 clinical trials: A single institution experience from 1999 to 2010

June Y. Hou [a,b,c], Santiago Aparo [a,b,d], Mohammad Ghalib [a,d], Imran Chaudhary [a,d], Umang Shah [a,d], Umang Swami [a,d,e], Mark Einstein [a,b,c], Gary L. Goldberg [a,b,c], Sridhar Mani [a,b,d], Sanjay Goel [a,b,d,*]

[a] Montefiore Medical Center, Bronx, NY, USA
[b] Albert Einstein College of Medicine, Bronx, NY, USA
[c] Department of Obstetrics & Gynecology, & Women's Health, Division of Gynecology Oncology, Albert Einstein College of Medicine, Bronx, NY, USA
[d] Department of Medical Oncology, Albert Einstein College of Medicine, Bronx, NY, USA
[e] Department of Radiology, Albert Einstein College of Medicine, Bronx, NY, USA

HIGHLIGHTS

- 58% of patients with gynecologic cancer achieved clinical benefit, and 9.2% experienced DLT in phase 1 trials.
- Albumin and absolute neutrophil count independently predict survival.
- Odds of achieving clinical benefit are associated with changes in albumin and LDH.

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ABSTRACT

Objectives. There is a scarcity of outcome data regarding phase 1 trials for patients with gynecologic malignancy. The objective of this study was to assess toxicity, clinical benefit and prognosticators in gynecologic oncology patients participating in phase 1 trials.

Methods. All phase 1 oncology trials conducted at Albert Einstein Cancer Center from 1999 to 2010 were reviewed and extracted for relevant demographic and clinical data concerning patients with gynecologic malignancy. Cox-proportional and logistic regression modeling were used for multivariate analysis.

Results. 120 distinct patients with gynecologic malignancy participated in 41 trials, constituting 30.6% of all phase 1 patients enrolled in the same time period. The median age is 59 years. Out of the 184 patients enrolled, 160 individual responses were evaluable. Seventeen DLT events (9.2%) occurred, including 1 (0.5%) treatment-related mortality. There were 27.2% ≥ grade 3 hematologic and 24.4% non-hematologic toxicity. Eighty patients had stable disease (SD, 50%), including 21.9% with SD ≥ 4 months, 11 (6.3%) with partial response (PR), and 3 (1.9%) achieving complete response (CR). The clinical benefit rate (CBR = SD + CR + PR) was 58.1%. Albumin (Alb) ≤ 3.5 g/dL and abnormal ANC were independent negative prognosticators of survival. We also found a continuous correlation between changes in Albumin ($p = 0.02$) and LDH ($p = 0.02$) and odds of achieving CBR ≥ 4 month.

Conclusions. Our clinical outcome and safety data suggested that phase 1 trials may be a reasonable option for patients with advanced and recurrent gynecologic cancer. The potential prognosticators identified should be further validated in larger trials.

Introduction

In the last ten years, there is a 143% increase in oncology drugs under active clinical research and development [1]. As an initial step in bringing novel therapeutics into clinical practice, phase 1 trials aim to assess clinical safety, toxicity and to establish maximum tolerated dose (MTD) of the drug. Once viewed upon as a last 'therapeutic' resort, with tumor response rates of approximately 5% and treatment-related mortality

* Corresponding author at: Albert Einstein College of Medicine, Department of Medical Oncology, Montefiore Medical Center, 1825 Eastchester Road, Bronx NY 10461. Fax: +1 718 904 2830.
E-mail address: sgoel@montefiore.org (S. Goel).

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rates of 0.5%, phase 1 trial raises ethical concerns regarding its high risk, and little, if any benefit for patients [2]. Yet in the past decade, improved pipeline of preclinical developments and changes in phase I designs, including phase I/II window trials and other combined MTD establishment/efficacy trials, contribute to the much increased tumor response rate (8.6–10.6%) and clinical benefit rate (45–53%) [3–5] that are reported in more recent analysis. The landscape change in our understanding of tolerability and response calls into question the 'therapeutic misconception' that is often synonymous with phase 1 trials, and may affect counseling of patients with advanced cancer.

Patients with metastatic or recurrent gynecologic malignancies often present as a therapeutic challenge to oncologists when disease becomes resistant to conventional cytotoxic chemotherapies. Declining performance status may be attributable to the increasing number of prior cytotoxic regimens, and is often associated with accumulating toxicities without apparent clinical benefit. There is a heightened awareness of the need for improving treatment strategies for these patients, with a focus on increasing efficacy as well as decreasing toxicity. In an era of rapid expansion in anti-cancer drug development that includes immunologic, biologic, and novel cytotoxic agents, many of which have different toxicity profiles when compared with non-specific cytotoxic therapy, it is important to gain a better understanding of patient outcome and safety, and to strive to identify prognostic markers. Herein, we report our experience with patients diagnosed with gynecologic malignancies who enrolled in phase 1 trials at Albert Einstein Cancer Center from 1999 to 2010.

Methods

Data source

Patients with pathologically confirmed gynecologic malignancies of all disease sites and histology that enrolled in phase 1 oncology trials conducted at Montefiore Medical Center and Albert Einstein Cancer Center from 1999 to 2010 are included in this analysis. All patient-related and treatment-related efficacy and toxicity information is abstracted from patient records, infusion records, laboratory testing, radiologic imaging, and flowcharts were abstracted.

Study participants

Patients are at least 18 years old with metastatic and/or unresectable disease that is refractory to standard curative treatments, and has evidence of measurable or evaluable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST). Further eligibility criteria specific to the types of trials are approved by the Institutional Review Board (IRB), and are available upon request.

Clinical outcome

Patients receiving at least one cycle of the specific agent, and undergoing at least one RECIST-based tumor response assessment are considered evaluable for response. A designated radiologist determines tumor response in accordance to RECIST criteria at time intervals as specified in the individual protocols. Overall survival (OS) is measured from date of enrollment in the phase 1 trial until death from any cause or last follow-up. Progression-free Survival (PFS) is defined from date of enrollment to date of documented progression of disease (PD). Clinical benefit rate (CBR) is defined as achieving at least one of the following three outcomes: 1) complete response (CR), 2) partial response (PR), and 3) stable disease (SD).

Toxicities are assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v. 2.0–4.0 depending on the dates the specific trial protocols were activated.

Statistical considerations

Grade 3 and 4 toxic events are calculated for participants according to disease site, or the trial category. Rates are obtained by dividing the total number of events (response, deaths, or grade 3/4 toxic events) by the total number of patients assessed for response or toxicity.

Descriptive statistics are used to characterize demographic and clinical parameters. In the univariate analysis, the X^2 test and Fisher exact test are used to examine association of categorical variables; and the student *t*-test and Mann–Whitney test are used for continuous variables. Cox-proportional and logistic regression modeling are used for multivariate analysis. Final models presented are checked for confounding and interactions. Kaplan–Meier method was used to report survival curves. All analyses are done using STATA 11.2 software (STATACorp LP).

Results

Patient characteristics

From 1999 to 2010, there are a total of 41 distinct phase 1 clinical therapeutic trials at the Montefiore Medical Center and Albert Einstein Cancer Center. Of the 602 enrolled phase 1 participants, 30.6% has gynecologic malignancies. There are 120 distinct patients, of which 19% participate in more than one trial, with a median of 2 trials per patient among this cohort (range 2–6), and account for a total of 184 enrollments. The median time from cancer diagnosis to

Table 1
Patient characteristics.

Characteristics	Number of patients (%)[a]
Age (years)	
<65	135 (73.4)
≥65	49 (26.6)
ECOG	
0	14 (7.6)
1	138 (75)
2	5 (2.7)
UK	27 (14.7)
Prior cytotoxic regimens	
1–3	80 (43.5)
≥4	104 (56.5)
Cancer site	
Epithelial ovary/FT/PPC	118 (64.2)
Uterus	40 (21.7)
Endometrioid	6 (3.3)
UPSC	10 (5.4)
Leiomyosarcoma	10(5.4)
carcinosarcoma	6 (3.3)
Others	8 (4.3)
Cervix	26 (14.1)
Squamous	12 (6.5)
Adenocarcinoma	13 (7.1)
Others	1(0.5)
Number of metastasis	
1–2 sites	101 (54.9)
≥3 sites	83 (45.1)
Metastatic site	
Lung	66 (35.9)
Liver	66 (35.9)
Lymph	82 (44.6)
Abdominal/pelvic mass	61 (33.2)
Prior surgery	
Yes	165 (89.7)
No/unknown	19 (10.3)
Prior radiation	
Yes	64 (34.8)
No	87 (47.3)
Unknown	33 (17.9)

Baseline characteristics of patients at time of enrollment.
[a] Total n = 184.