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A phase I study of intermediate dose cytarabine in combination with lenalidomide in relapsed/refractory acute myeloid leukemia

Elizabeth A. Griffiths[a,*], William E. Brady[b], Wei Tan[b], Carlos E. Vigil[a], James E. Thompson[a], Laurie A. Ford[a,c], Noelle M. Dickey[a,c], Heather L. Bashaw[a,c], Jill Sperrazza[a], Meir Wetzler[a], Eunice S. Wang[a]

[a] Department of Medicine, Roswell Park Cancer Institute, Elm & Carlton Sts, Buffalo, NY 14263, United States
[b] Department of Biostatistics & Bioinformatics, Roswell Park Cancer Institute, Elm & Carlton Sts, Buffalo, NY 14263, United States
[c] Clinical Research Services, Roswell Park Cancer Institute, Elm & Carlton Sts, Buffalo, NY 14263, United States

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ABSTRACT

Relapsed/refractory (r/r) Acute Myeloid Leukemia (AML) remains a therapeutic challenge. Cytarabine arabinoside (AraC) forms the backbone of most regimens, with complete responses (CR) ranging from 17 to 20%. Lenalidomide (Len) is approved by the FDA for multiple myeloma and myelodysplasia and has demonstrated activity in AML. We developed a phase I study to evaluate the safety and tolerability of Len in combination with intermediate dose AraC (1.5 g/m^2/day given on days 1–5) in adults with r/r AML. The maximally tolerated dose for this combination was 10 mg daily on days 6–26 of a 28 day cycle. Dose de-escalation from 25 mg was required due to rash, liver function abnormalities, and hypokalemia. Of 32 evaluable patients, five achieved CR (16%), 5CRi (16%) and 3 had hematological improvements for an overall response rate of 41% (13/32). Median overall survival (95% confidence interval) for patients treated on study was 5.8 (2.5–10.6) months and disease free survival was 3.4 (2.3–6.2) months. This single institute phase I trial of Len and intermediate dose AraC was associated with marked skin and other toxicities. At the dose and schedule tested, this combination did not appear to result in improved CR over single agent AraC for r/r AML.

1. Introduction

The incidence of acute myeloid leukemia (AML) in the United States is about 20,000 cases per year with a five year survival rate around 25% [1,2]. A majority of AML related deaths result from disease relapse [2,3]. Although significant strides have been made in the identification and appropriate management of selected better risk patients with AML, any patient who develops a relapse is likely to die of their disease [2,3]. Patients with primarily refractory AML have an overwhelmingly poor rate of survival [3]. Allogenic bone marrow transplantation can salvage a minority of very fit patients with an available donor but even among the selected patients who are able to receive a transplant, relapse remains a serious problem [3]. This population of relapsed and refractory (r/r) AML patients is a considerable therapeutic challenge and a majority of practicing leukemia physicians would recommend an early phase clinical trial in this setting [3]. Cyarabine arabinoside (AraC) is the most active drug in the management of AML, and it forms the backbone of a majority of r/r regimens [3–8]. Despite this, the benchmark response to single agent AraC (at a variety of different doses and schedules) in the r/r setting remains a dismal 17–20% [9]. Unfortunately, despite intense study, a large number of trials in the setting of r/r disease have failed to demonstrate substantive improvements relative to single agent intermediate dose AraC, and thus the population of patients with r/r AML represents a very real unmet medical need [3].

The immunomodulatory drug Lenalidomide (Len), is approved by the US Food and Drug Administration for multiple myeloma and 5q-myelodysplasia. Blum and colleagues demonstrated single agent activity in r/r AML at doses as high as 50 mg for 21 days (d) of a 28 day cycle with a response rate of 16% (5/31; all responses were complete (CR) at doses between 25 and 50 mg) [10]. Fatigue was the dose limiting factor in this study. Importantly, responses were associated with clearance of cytogenetic abnormalities and were durable, lasting between 5.6 and 14 months. Single agent high dose Len (50 mg/day for 28 days × 2 cycles followed by 10 mg main-

* Corresponding author at: Department of Medicine, Roswell Park Cancer Institute, Elm & Carlton Sts, Buffalo, NY 14263, United States.
E-mail address: elizabeth.griffiths@roswellpark.org (E.A. Griffiths).

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tenance) has also been studied as upfront therapy in a population of older adults with AML and this approach was associated with a 30% (10/33) combined CR/incomplete CR (CRi) rate per International Working Group Criteria [11]. The median CR/CRi duration was 10 (range, 1–17) months. Reasons for treatment discontinuation were disease progression, adverse events and patient preference. The 60-day mortality was 27% (9/33) with seven of these deaths occurring due to disease progression.

The combination of Len with intensive therapy as initial treatment for AML has also been explored [12–14]. Len has been combined with AraC at 200 mg/m^2 for seven days and daunorubicin at 45 mg/m^2 for three days with provisions to increase daunorubicin to 60 mg/m^2 if tolerated. Len was used at a dose of 10 mg/day (days 1–21) and dose escalated to 25 mg/day (days 1–21) in a final cohort of 19 patients; consolidation therapy was given with Ara-C, daunorubicin and Len followed by single agent Len maintenance (10–25 mg/day) [12,13]. The rationale for the maintenance stems from Len's immune regulatory effects [15]. The preliminary results from this study revealed an overall response rate of 61% (46% (38/82) CR, 5% (4/82) CRi, and 10% (8/82) PR) associated with a median survival of 7.1 months (95%CI: 6.5–9.4) [13]. Major toxicities associated with the combination included elevated transaminases, elevated creatinine and lung disease associated with sepsis. Liver toxicity was deemed dose limiting at the 25 mg dose level. Another study examining Len with high dose chemotherapy in patients with high grade MDS or AML specified pre-treatment with Len 10 mg for 21/28 days (n = 14) followed by bone marrow evaluation. Nine patients (64%) went on to receive Len 10 mg days 1–10 in combination with ADE (Cytarabine 100 mg/m^2 twice daily IV for 10 days, Daunorubicin 50 mg/m^2 days 1,3, and 5 IV and Etoposide 100 mg/m^2 daily days 1–5 IV). The response rate in this study was 44% (2 patients had CR, 1 had CRi and 1 had a PR); 2 patients went on to receive allogenic transplant (Allo Tx) in remission, the remainder discontinued therapy due to disease progression, failure of hematologic recovery or death.

The mechanism of action of Len in AML is incompletely understood, although it has previously been shown to decrease cell proliferation, enhance apoptosis, interrupt tumor-stroma interactions and alter innate and adaptive immune responses [16]. More recently the mechanism of action in patients with del(5q) myelodysplastic syndrome and multiple myeloma has been demonstrated to depend on enhanced ubiquitination and degradation of specific protein targets, opening the door to therapeutic combinations that target protein/protein interaction, although this mechanism has yet to be demonstrated in AML [17–19]. Preclinical testing prior to the recognition of this mechanism, suggested a potential synergistic effect for the combination of Len with AraC [20].

Based upon the prior evidence of single agent activity in the r/r setting, the reported high response rates for upfront combination therapy, and the *in vitro* suggestions of synergy, we developed a phase I study to evaluate the safety and tolerability of Len in combination with intermediate dose AraC, one of the most active approaches in r/r AML [9].

2. Patients and methods

The study (#NCT01246622) was conducted in accordance with the Declaration of Helsinki, approved by the Roswell Park Cancer Institute Review Board, and all patients provided written informed consent. Eligible patients were older than 18 years of age with a confirmed pathologic diagnosis of AML which had recurred or was refractory to at least one prior line of therapy. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status >2 and adequate renal and hepatic function [21]. Patients were excluded if they had active central nervous system disease, uncontrolled systemic infections, congestive heart failure, adrenal insufficiency, any anti-cancer therapy within 14 days of enrollment, or prior exposure to Len. All enrolled patients had to agree to practice appropriate contraception. The study initially planned to treat patients with intermediate dose AraC 1.5 g/m^2/day over 3 h on days 1–5 with initiation of Len on days 6–10 of a 28-day cycle. Shortly after study initiation, several manuscripts were published suggesting the superiority of more prolonged Len exposure, and the study was therefore amended to extend the Len dosing interval [12–14]. After study amendment, patients could receive one or two courses of induction therapy consisting of AraC 1.5 g/m^2/day over 3 h on days 1–5 with initiation of daily Len on days 6–26 of a 28-day cycle, using a standard 3 + 3 dose escalation/de-escalation schema. Days 27–28 were rest days and a bone marrow biopsy was performed on day 28 of induction cycles 1, 2 for response evaluation. Patients with ≥5% blasts in the blood or bone marrow, who had resolution of study related toxicities and a stable or decreased bone marrow blast percentage, could receive a second identical cycle of therapy on study starting on or after day 29 of cycle 1. Patients who failed to achieve these endpoints were deemed to have failed study therapy. Those who achieved CR with 1 or 2 cycles of induction were maintained on Len 10 mg orally daily on a 28 day cycle with bone marrow biopsy for continued response assessment performed every 3 months. Maintenance cycles were to be dose delayed for neutropenia (ANC < 1000/uL), thrombocytopenia (platelets < 50,000/uL), drug related rash/neutropenia > grade 1 or any drug related adverse events > grade 2. The primary objective of the study was to determine the maximum tolerated dose (MTD) of Len following intermediate dose AraC in patients with r/r AML. The secondary endpoint was evaluation of the efficacy of this regimen. The initial study schema with Len dosed on days 6–10 (dose level 1) was abandoned after the enrollment of 4 patients. Dose level 1A was 25 mg days 6–26 and dose escalation was planned to dose levels 2 (30 mg), 3 (35 mg) and 4 (50 mg); dose de-escalation was also provided for with dose level −1 set at 15 mg and dose level −2 at 10 mg. The dose limiting toxicity (DLT) period was defined as the first 28 days of the first induction cycle. DLT was defined as grade 3 or higher non-hematologic or non-infectious toxicities occurring during cycle 1 of therapy only; neither hematologic nor infectious toxicities were considered dose limiting. Failure of count recovery by day 42 was also not included as a DLT. Responses were assessed by International Working Group Criteria for AML and MDS [22,23]. Up to 24 patients could be enrolled in the dose escalation phase with an additional 12 patient expanded cohort at the maximum tolerated dose (MTD) for further evaluation of efficacy; patients who failed to complete 80% of study medication were replaced in all cohorts. A schema of the study design is presented in Fig. 1.

3. Results

3.1. Patients

A total of 51 patients were consented to this study from February 2011 to May 2014. Forty-five patients were deemed eligible and were subsequently enrolled on study. Six patients failed eligibility screening due to inadequate creatinine clearance (n = 2), elevated baseline liver function tests (n = 1), active infection precluding study entry (n = 1), non-AML diagnosis (n = 1), or inadequate ejection fraction (n = 1). All 45 treated patients were evaluated for toxicity. Thirty-two patients were evaluable for response; the remaining 13 patients were not response-evaluable due to inadequate compliance with 80% of study therapy. Clinically relevant patient characteristics are detailed in Table 1. Approximately half the patients were female (20/45). The median age was 66 year