Leukemia Research Reports 7 (2017) 14–16

Contents lists available at ScienceDirect

Leukemia Research Reports

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

Clofarabine desensitization: A case report Leukemia research reports

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ARTICLE INFO

Keywords:
Clofarabine
Acute Myeloid Leukemia
Desensitization

ABSTRACT

We describe a relapsed AML patient who had two prior severe reactions to clofarabine involving rigors, emesis, tachycardia, hypotension, and acute kidney injury. Given previous prolonged remission achieved with clofarabine and cytarabine therapy years prior, rechallenge was undertaken upon discovery of AML relapse. We designed a desensitization protocol performed with the first dose of clofarabine, leading to successful administration of the entire clofarabine/cytarabine treatment course. From this case we show promise for clofarabine rechallenge after prior hypersensitivity reactions in patients with few treatment options for relapsed AML.

1. Introduction

Clofarabine, a purine nucleoside analog of cladribine, is used in adult and pediatric regimens to treat Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL). Use of clofarabine has been studied as monotherapy [1] and in combination with cytarabine [2,3] or idarubicin [3]. It is incorporated into the DNA of tumor cells, causing termination of DNA synthesis resulting in apoptosis. The well-established toxicities of clofarabine include myelosuppression, capillary leak syndrome (in 1–4% of patients), elevated hepatic enzyme levels, and nausea [4].

Clofarabine-associated capillary leak syndrome, attributed to cytokine release, is characterized by hypotension, tachycardia, and tachypnea, and can be fatal. Alternatively, Type I hypersensitivity to clofarabine can occur in up to 5% of patients, and is also a contraindication to further therapy per product labeling [4]. In practice, reactions to clofarabine often result in discontinuation of a therapy which may otherwise provide complete responses in patients treated for AML. However, attempts at clofarabine desensitization have not been previously described in the literature.

2. Case report

Here we report successful clofarabine desensitization in a 76-year-old male patient with AML. His comorbidities include Type II diabetes, hypertension, and a history of acute illness induced cardiomyopathy that has resolved. The patient was diagnosed with AML in 2012. After no response to azacitidine therapy in 9/2012 he was treated with clofarabine 20 mg/m^2 Days 1–5+ cytarabine 20 mg subcutaneously twice daily Days 1–10 based on the Faderl *Cancer* 2012 study [5] in the hopes of achieving a complete remission and moving on to stem cell transplantation. He achieved his first complete response (CR1). However, he developed cardiomyopathy with a drop in ejection fraction to 20% and thus was no longer eligible to proceed with stem cell transplant. His age of greater than 70 precluded standard high dose cytarabine consolidation, thus “maintenance” therapy to prolong his initial remission was discussed. Based on small series suggesting successful azacitidine maintenance post CR [6], he was treated with azacitidine Days 1–5 of a 28 day cycle off study through 9/2014.

He did well until 9/2014 at which time a surveillance bone marrow revealed his first relapse with low volume disease of < 10% blasts. Attempts at increasing the schedule of azacitidine to the standard 7-day schedule every 28 days were not successful in regaining remission. Subsequently, given a 2 year remission from his first round of clofarabine + cytarabine induction + azacitidine maintenance and ongoing good performance status he was re-induced with the same regimen in 11/2014. He achieved CR2 with the first induction of clofarabine Days 1–5 + cytarabine Days 1–10. With this treatment round, the entire Faderl approach was used, as described in the 2012 publication [5,7]. Per protocol, once complete remission is achieved, patients go on to receive two abbreviated courses of clofarabine Days 1–3 + cytarabine Days 1–7 consolidation. During his first clofarabine + cytarabine consolidation in January 2015 he only received 2 doses of the clofarabine due to an episode of hypotension and vomiting and the

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http://dx.doi.org/10.1016/j.lrr.2017.02.001
Received 1 December 2016; Received in revised form 6 February 2017; Accepted 12 February 2017
Available online 13 February 2017

Table 1
Clofarabine desensitization protocol.

Clofarabine Desensitization Protocol (Dose =48 mg [20 mg/m^2])							
Dose	**Dose**	**mL Required [Solution]**	**Volume (0.9% Sodium Chloride)**	**Fraction of Total Dose**	**Administration**	**Cumulative Dose (per mg)**	**Cumulative Dose (per m^2)**
1a	0.048 mg	**0.48 mL (of 0.1 mg/mL dilution)**	100 mL	1/1000	Day 1, over 90 min	0.048 mg	0.04 mg/m^2
1b	0.48 mg	**4.8 mL (of 0.1 mg/mL dilution)**	100 mL	1/100	Day 1, over 90 min	0.53 mg	0.24 mg/m^2
1c	4.8 mg	**4.8 mL (of 1 mg/mL)**	100 mL	1/10	Day 1, over 90 min	5.3 mg	2.24 mg/m^2
1d	42.67 mg	**42.67 mL (of 1 mg/mL)**	100 mL	Remainder of first dose	Day 1, over 90 min	48 mg	20 mg/m^2
2	48 mg	**48 mL (of 1 mg/mL)**	100 mL	100% of dose	Day 2–5, over 2 h	48 mg	20 mg/m^2

development of acute kidney injury (AKI) after the second dose. He completed all 7 days of the cytarabine. He then was readmitted in February 2015 for the second consolidation clofarabine + cytarabine per protocol. He unfortunately developed a severe reaction occurring after Day 1 of the two-hour clofarabine infusion including rigors, hypotension (systolic blood pressure between 70 and 80 mmHg), six episodes of emesis, tachycardia leading to demand-related ischemia and mild troponin elevation, and low urine output resulting in AKI with a peak serum creatinine of 1.5 mg/dL. Clofarabine therapy was discontinued as his reaction was felt to be consistent with a combination of components of both clofarabine-induced capillary leak syndrome and an allergic reaction. Cytarabine was held, and the first dose was administered two days later following recovery from the clofarabine reaction. He recovered from this episode without long term toxicity and remained in CR2. He then went on to decitabine maintenance, per the Faderl protocol, without the intermittent protocol defined clofarabine + cytarabine maintenance cycles. He continued to do well until counts dropped in 8/2016. Repeat bone marrow biopsy then documented AML relapse number 2.

Upon discovery of this AML relapse in 8/2016, extensive discussion ensued. Given his excellent performance status, the lack of good clinical trial options that he was eligible for, and his prior prolonged remissions with clofarabine + cytarabine, the possibility of clofarabine desensitization was raised. After presenting the patient with the options, the decision was made to attempt re-induction therapy again with clofarabine + cytarabine. We designed a desensitization protocol for the administration of clofarabine, described in Table 1. The protocol was based on existing protocols for carboplatin desensitization at our institution. Pre-medications included ondansetron 16 mg by mouth, ranitidine 50 mg intravenously, acetaminophen 650 mg by mouth, diphenhydramine 50 mg by mouth, and dexamethasone 12 mg by mouth. All nephrotoxic medications, or those likely to contribute to AKI, were held. Vital signs were obtained every 15 min during infusion. During the last ten minutes of the first clofarabine infusion, the patient experienced mild rigors. Vital signs remained stable. He was given warm blankets and the rigors subsided. No medications were required to alleviate the mild reaction. All remaining doses of clofarabine were subsequently infused per standard rates without incident, and the patient was discharged from the hospital to home at the conclusion of chemotherapy. Four weeks later, the post-re-induction bone marrow biopsy showed no evidence of AML.

3. Discussion

Case reports of successful chemotherapy desensitizations have been described for platinum agents, taxanes, anthracyclines, rituximab [8], and cytarabine [9], but not specifically clofarabine. For older patients with relapsed AML that are not candidates to receive anthracycline therapy, options include clofarabine/cytarabine, hypomethylating agents, and low-dose cytarabine [10], which gives the clinician relatively few treatment options aside from clinical trial enrollment. Thus it may be preferable to maintain the option of using clofarabine despite encountering capillary-leak syndrome or hypersensitivity during administration. Our successful desensitization approach avoided a severe reaction and led to a favorable response in this patient.

As with any desensitization, the decision to retry therapy must be approached cautiously, especially if capillary leak syndrome alone is suspected in the absence of hypersensitivity. Batzlaff and Dulohery recently presented a case of clofarabine-induced capillary leak syndrome in a 70-year-old patient with AML, who experienced tachycardia, hypotension, and renal injury leading to death [11]. Capillary leak syndrome and clofarabine hypersensitivity have common signs [12]; however, inflammatory responses to clofarabine leading to endothelial injury thought to result in capillary leak syndrome [13] present after several days of therapy [11–13]. Elements of both capillary leak syndrome as well as an allergic reaction were felt to be present in our patient [14]. Though drug desensitization protocols are meant to stave off immediate hypersensitivity reactions, it is possible that this approach could also reduce the cytokine release which provokes symptoms of capillary leak syndrome.

Prior studies show clofarabine-associated AKI with higher doses of 30–40 mg/m^2; Faderl et al. reported a 5% incidence of Grade 3 or 4 acute renal failure [15]. Younger patients with better baseline renal function are less likely to experience AKI with clofarabine [16]. In our patient, AKI occurred previously in the setting of dehydration, concomitant angiotensin-converting enzyme inhibitor and metformin use, and hypotension. During desensitization we ensured that good hydration was maintained, lisinopril and metformin were held, and clofarabine-induced hypotension was avoided, all of which likely contributed to the absence of AKI during the process.

In summary, clofarabine therapy following prior hypersensitivity and capillary leak syndrome was feasible upon implementation of a clofarabine desensitization protocol for AML re-induction therapy. The desensitization regimen was only performed once with the first dose, and subsequent doses were infused without any complications at the standard rates. The outcome of this case shows promise for clofarabine challenges and desensitization attempts in relapsed patients with few other treatment options.

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