

RESEARCH ARTICLE

Clofarabine in the Treatment of Elderly Patients with Acute Myeloid Leukemia

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Abstract

Background: Elderly patients with acute myeloid leukemia (AML) have a poor outcome because of co-morbidities, poor tolerance to intensive chemotherapy and inherently more resistant disease. Clofarabine is a second generation nucleoside analogue which has shown promising activity in elderly patients with AML. This study was conducted to review the outcome of treatment with clofarabine in a group of such patients. **Methods:** The records of 5 elderly patients who were diagnosed to have AML and treated with clofarabine over a 12 month period were reviewed retrospectively. **Results:** There were 2 female and 3 male patients with a median age of 68 years (range 65-82). At the time of treatment, 2 patients had newly diagnosed AML not considered suitable for intensive therapy, while 3 patients had partial or no response to conventional chemotherapy. The overall response rate was 100%, all patients achieving a complete remission. Induction and consolidation were well tolerated. All patients developed neutropenia with a median duration of 20 days (range 17-42). One patient developed hand and foot syndrome and a generalized rash but recovered. There was no mortality and all patients remained in remission after a median follow-up of 5.2 months (Range 3-10). **Conclusion:** Clofarabine (alone or in combination) is active in elderly AML patients with an acceptable safety profile and should be considered a potential option in this group.

Keywords: Acute myeloid leukemia - clofarabine - elderly

Asian Pacific J Cancer Prev, 14 (2), 1089-1092

Introduction

Treatment of acute myeloid leukemia (AML) remains unsatisfactory in the elderly patients. These patients respond poorly to conventional chemotherapy and apart from the presence of co-morbidities and generally poor tolerability to chemotherapy, poor response to chemotherapy appears to be due to differences in the biologic characteristics of AML in the elderly as compared to the younger patients (Kantarjian et al., 2010). Elderly AML patients have a higher frequency of unfavorable cytogenetics, MDR1 protein expression, and functional drug efflux; each of these factors occurring more frequently in both de novo and secondary AML (Leith et al., 1997; Gupta et al., 2005). Although risk factors and decision criteria for intensive chemotherapy in older patients with AML have been recognized, they are not very helpful in clinical practice as majority of the patients are not eligible to receive this form of therapy (Malfuson et al., 2010). For this reason there is an urgent need for novel strategies and new therapies for the elderly patients with AML.

Clofarabine (2-chloro-2-fluoro-deoxy-9-D-

arabinofuranosyladenine) is a second generation nucleoside analog which has the favorable pharmacokinetic properties of fludarabine and cladribine (Montgomery et al., 1992). It inhibits DNA repair and activates the mitochondrial apoptotic pathway leading to cell death (Xie and Plunkett, 1996; Parker et al., 2003). Clofarabine showed promising activity in phase 1 and 2 studies in patients with relapsed and refractory acute leukemias in adults and children. (Kantarjian et al., 2003a; 2003b; Jeha et al., 2004; Styczynski et al., 2009). Clofarabine has also shown activity in combination with high dose ARA-C in relapsed or refractory younger and older patients with AML (Tse et al., 2011).

Most of the studies published previously come from limited centers from the US or Europe and there is a lack of experience with this drug in the community setting (Krawczyk et al., 2010). Here we describe our experience in the elderly AML patients treated with clofarabine.

Materials and Methods

The records of 5 AML patients older than 60 years who were treated with clofarabine over a 12 month period,

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Table 1. Characteristics of the Patients

No	Age	Sex	FAB subtype	Performance status*	Karyotype	Primary or Secondary AML	Co-morbid conditions	EF%	Follow-up (months)
1	73	F	M0	III	Normal	De novo	DM/HTN	58	10
2	65	M	M6	II	Trisomy-8	Secondary (MDS)	DM/HTN	54	3
3	82	M	M1	III	Normal	De novo	DM/HTN/ IHD/RA	34	5
4	68	F	M0	III	Deletion 7q	Secondary (MDS)	DM/HTN/ IHD/PVD	40	6
5	65	M	M2	III	Normal	Secondary	DM/HTN/ IHD/COPD	38	4

*Eastern Cooperative oncology group (ECOG) performance status, MDS=myelodysplasia, DM=diabetes mellitus, HTN=hypertension, IHD=ischemic heart disease, RA=rheumatoid arthritis, PVD=peripheral vascular disease, EF=ejection fraction

were reviewed retrospectively (October 2011-september 2012). Data were collected from the patients' charts, computerized records and laboratory results. Diagnosis of AML was based on morphology and immunophenotyping of the bone marrow according to the WHO criteria, and cytogenetic analysis was performed by standard methods. Two patients had newly diagnosed AML and 3 patients had received previous chemotherapy; two of them had refractory disease and the third patient had a partial response to therapy. Clofarabine was infused over 1-2 hour and adequate hydration was given prior to its administration. Clofarabine was generally given for 5-days, either alone or in combination with other drugs. Patients received supportive measures as and when required and included intravenous fluids, allopurinol, antibiotics, blood products, and granulocyte colony stimulating factor (G-CSF). Patients were monitored with complete blood count (CBC) and biochemistry profile at least three times weekly and other investigations were performed as clinically dictated.

Assessment of the response was carried out by bone marrow examination around day 28 of induction, and thereafter as deemed necessary. Patients received consolidation courses after confirmation of remission and recovery of the absolute neutrophil count (ANC) to $\geq 1.0 \times 10^9/l$ and platelet count to $\geq 75 \times 10^9/l$. Final assessment for the study was based on the last review of patients before the data collection.

Results

Characteristics of the 5 AML patients treated with clofarabine are shown in Table 1. There were 2 female and 3 male patients with a median age of 68 years (range 65-82). The FAB subtypes of AML are given in Table 1. Cytogenetic results were abnormal in 2 patients and normal in 3 patients. Three patients had high risk disease. Two patients received the treatment as first line therapy and 3 patients had an unsatisfactory response (refractory or partial response) to previous therapy (low dose Ara-C with liposomal doxorubicin in one case, 3+7 and 2+5 regimens in second and third case, respectively). The chemotherapy regimens and the doses of clofarabine and other drugs are given in Table 2.

Clofarabine (alone or in combination) was reasonably tolerated. As expected, all patients developed grade 3-4 neutropenia with a median duration of 20 days (range 17-42) and episodes of febrile neutropenia. One patient developed hand and foot syndrome and a generalized rash (palmar-plantar erythrodysesthesia) but recovered. This

Table 2. Clofarabine Schedule, Chemotherapy Regimens and the Outcome

Patient No.	Chemotherapy regimens	Outcome and further treatment
1 Induction:	ARA-C 20 mg/m ² subcutaneous day1-14+ liposomal doxorubicin 60 mg on day-1	No remission
Re-induction:	Clofarabine 30 mg/m ² IV day 1-5	Remission
Consolidation:	-	2 courses x q4 weekly
2 Induction:	ARA-C IV + idarubicin (2+5)	Residual disease day 28
Re-induction:	Clofarabine alone 40 mg/m ² IV day1-5	Remission day 28
Consolidation:	Clofarabine 30 mg/m ² IV day 1-5	2 courses x q4 weekly
3 Induction:	ARA-C IV + idarubicin (3+7)	Residual disease day 28
Re-Induction:	Clofarabine 40 mg/m ² IV day 1-5	Remission Day 28
Consolidation:	Clofarabine 30 mg/m ² IV day 1-5	Receiving 2 nd consolidation
4 Induction:	Clofarabine 40 mg/m ² IV day 1-5	Remission day 28
Consolidation:	Clofarabine 30 mg/m ² IV day 1-5	2 courses q4 weekly
5 Induction:	Clofarabine 40 mg/m ² IV day 1-5	Remission day 28
Consolidation:	Clofarabine 30 mg/m ² IV day 1-5	2 courses q4 weekly

Table 3. Toxicity Profile and Side Effects Suffered by the Patients

Toxicity & side effect [§]	Patient				
	1	2	3	4	5
Neutropenia	4	4	4	4	4
Thrombocytopenia	4	4	4	4	4
Mucositis	3	2	3	2	3
Skin rash	1	3	1	2	1
Hand & foot syndrome	-	3	1	-	-
Sepsis	1	2	1	4	1
Bacterial infection	1	2	1	3	1
Fungal infection	-	-	1	1	-
Heart failure [§]	II	1	III	II	I
Hyperbilirubinemia	-	1	-	1	-
Raised liver enzymes	1	-	-	1	1
Vomiting	2	2	2	1	1
Diarrhoea	-	2	-	-	1

*Toxicity described is the maximum toxicity suffered in any of the courses of therapy, [§]WHO grades of toxicity 1-4, [§]New York Heart Association class of heart failure

complication did not develop in the subsequent clofarabine cycles. There was no mortality and all patients remained in remission at the time of data collection, after a median follow-up of 5 months (Range 3-10). The details of the toxicities suffered by the patients are shown in Table 3.

Discussion

Acute myeloid leukemia (AML) is a disease of the old age, with a median age around 65 years at diagnosis (Kantarjian et al., 2010). Treatment outcomes of AML in the elderly patients remain disappointing with poor overall survival. Few elderly patients are able to receive conventional induction chemotherapy regimens due to poor tolerability and presence of co-morbidities (Kantarjian et al., 2010). Even in patients who are able

to tolerate conventional chemotherapy, remission and survival rates remain inferior as compared to younger patients because of inherently more resistant disease (Leith et al, 1997; Gupta et al., 2005). Complete remission rates in older patients may be as low as 30% by using the usual standard induction (“3+7”, cytarabine plus an anthracycline) chemotherapy regimens and remissions are usually of short duration and rarely last more than one year. The median time from treatment to death is 5-10 months and the overall survival remains approximately 10% (Godwin and Smith., 2003; Rowe and Tallman., 2010). In view of this, there is an urgent need for newer drugs and alternative therapies in this patient population.

Clofarabine, a second generation nucleoside analog, has shown activity in patients with relapsed or refractory acute myeloid leukemia in younger and older patients as a single agent and in combination with high dose ARA-C. (Kantarjian et al., 2010; Krawczyk et al., 2010; Tse et al., 2011). A recent review of clofarabine in the elderly patients with AML revealed that clofarabine may be appropriate in a subset of patients with poor performance status and cardiovascular disease, not fit for intensive chemotherapy (Tran and Yang, 2012). Compared to single-agent clofarabine, response rates and median OS were higher for clofarabine combined with cytarabine, albeit with somewhat increased toxicity. Clofarabine also appeared to generate good responses in high risk cytogenetic patients (Burnett et al., 2010; Kantarjian et al., 2010). For this reason, addition of clofarabine to the AML therapy in the elderly patients has generated some enthusiasm in hemato-oncologists taking care of these patients.

Our limited experience shows that clofarabine alone or in combination with ARA-C is reasonably tolerated by the elderly patients with AML, and was also active in patients not responsive to other regimens. Three patients were either refractory to earlier regimens or had residual disease. All these patients achieved remission with clofarabine re-induction.

Although clofarabine has been evaluated in combination with ARA-C in low dose and high dose (Faderl et al., 2006; Faderl et al., 2008; Agura et al., 2011), there are no large scale studies of clofarabine in combination with conventional chemotherapy regimens and the standard dose Ara-C as in the “3+7” or reduced dose “2+5” regimen (cytarabine plus an anthracycline). Additional studies, particularly randomized controlled trials are needed to compare the efficacy of clofarabine with that of conventional chemotherapy regimens and to further evaluate the potential benefit of combining clofarabine with cytarabine.

In conclusion, clofarabine is useful in the elderly patients with AML with a favourable safety profile and should be considered an option in this group of patients.

Acknowledgements

This study was supported by the College of Medicine Research Center, Deanship of Scientific Research, King Saud University, Riyadh, Saudi Arabia

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