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Clofarabine-based regimen as useful bridge therapy for stem cell transplantation in refractory or relapsed pediatric leukemia

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ABSTRACT

Acute leukemia is often regarded as a popular malignancy affecting children. Noticeable enhancements in the treatment of childhood acute lymphoblastic leukemia, as well as acute myeloid leukemia have resulted in an upsurge in the cure rates. Presently, 80% of the children affected by acute lymphoblastic leukemia and 50% of those affected by acute myeloid leukemia can benefit from long-term remission. However, salvage routines have been very poor in some cases. Some of these cases include those that entail primary refractory disease, multiple relapses, as well as early systematic relapse. Relapsed leukemia is the fourth most popular malignancy affecting children, and there is need to develop novel therapeutic alternatives that can cater for this primary group of patients. With this perspective in mind, clofarabine remains to be the original and only anticancer drug that was certified for use in children and has been in use for over 10 years even before it was actually used in adults. There is need to include clofarabine in reduced-intensity conditioning (RIC) allogenic hematopoietic stem cell transplantation (HSCT) in the treatment of severe leukemia. Such an inclusion could possibly enhance the treatment outcomes. It is also necessary to design research that can examine the outcome of clofarabine based regimen as bridge therapy to stem cell transplant in young patients with refractory or relapsed leukemias.

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INTRODUCTION

Acute leukemia is characterized as one of the most popular pediatric malignancy. In the recent years, there has been a noticeable improvement in the cure rates for this condition. These improvements have largely been due to changes in frontier treatment protocols for childhood acute lymphoblastic leukemia (ALL) as well as acute myeloid leukemia (AML). At present, continuing remission is possible in about 80% of the pediatrics affected by acute lymphoblastic leukemia and about half of those affected with acute myeloid leukemia (Pession *et al.*, 2010). Neverthelesss, the outcome is usually dismal in cases where primary refractory disease, multiple relapses or early systematic relapse are involved. Since relapsed leukemia exemplifies the fourth most popular pediatric malignancy, it is important to develop new options for therapy covering this critical group of patients. In this regard, clofarabine is the leading and only anticancer drug

that is authorized for use in children before it was used in adults for a period of over 10 years. The drug is predominantly indicated as a single agent that can help with the treatment of pediatric patients aged between 1 and 21 years. Clofarabine can be used on patients with relapsed or refractory acute lymphoblastic leukemia after a minimum of two previous regimens (Pession *et al.*, 2010). In December 2004, the US Food and Drug Administration certified the drug. The certification by the FDA was based on the induction of comprehensive responses (Ghanem *et al.*, 2013). Additionally, the European Medicinal Evaluation Agency approved the drug in May 2006 (Pession *et al.*, 2010).

Clofarabine refers to a second-generation purine nucleoside analogue that had been designed rationally. The structure of the drug is meant to overwhelm the limitations and integrate the best qualities of cladribine and fludarabine. Clofarabine was, therefore, created depending on the experience with previous deoxyadenosine analogs fludarabine as well as cladribine. Both fludarabine and cladribine are used to facilitate the treatment of hematologic malignancies (Ghanem *et al.*, 2013). Generally, the drug is chemically represented by: (2-chloro-9-[2′-deoxy-2′-fluoro-β-D-arabinofuranosyl]-9H-purine-6-amine; Cl-F-ara-A; CAFdA). From the chemical structure, it is apparent that the drug has a chloro-group at the 2-position of adenine. As a result, the chemical structure of the drug is more carefully similar to that of cladribine than to fludarabine. Halogenation occurring at the 2-poisition of adenine makes this group of compounds impervious to intracellular deprivation by the adenosine deaminase enzyme. In the chemical structure of the drug, it is also clear that the fluorine at the C-2' position of the arabinofuranosyl moiety of clofarabine is substituted. The substitution is important since it enhances the steadiness in gastric acid and reduces its vulnerability to phosphorolytic cleavage by *Escherichia coli* enzyme in the gastrointestinal tract. These two can result in heightened oral bioavailability. The pharmacologic features of clofarabine bestow various advantages to the drug in comparison to fludarabine and cladribine. First, these features result in improved resistance towards deamination and phosphorolysis, thereby promoting improved stability. Second, the features contribute to an improved desire to deoxycytidine kinase (dCyd). Third, the features contribute to sustained retention of the triphosphate compound found in leukemic blasts. Fourth, the features contribute to the potent inhibition of the synthesis of DNA as well as ribonucleotide reductase (RNR) (Ghanem *et al.*, 2013).

Clofarabine has indicated cytotoxicity to various human tumor cell lines obtained from malignancies associated with hematology and solid tumor. The drug is also a compelling inhibitor of the L1210 mouse leukemia as well as K562 chronic myeloid leukemia (CML) blast cell lines. Exposure to clofarabine of 5 μM for a period of 72 hours repressed the growth of K562 cells by 50%. Incubation of clofarabine of approximately 50 μM for a period of 4 hours impeded the amalgamation of thymidine into DNA by about 50%. A depressing effect is also expected on deoxyadenosine triphosphate (TP), deoxycytidine TP, and deoxyguanine TP when clofarabine was incubated for 4 hours in quantities of 0.1 μM, 1.0 μM, or 10 μM. However, deoxythymidine TP pools were not affected with these quantities. Solid tumor cells have a higher sensitivity to clofarabine compared to fludarabine. More so, leukemic cell lines have a more favorable sensitivity when equaled to cladribine (Faderl *et al.*, 2005).

In some cases, clofarabine has been used together with cytarabine as a substitute treatment for patients with de novo, relapsed, or rather refractory severe myeloid leukemia. In other cases, the two drugs have been used a conditioning treatment for allogenic bone marrow transplantation. Existing guidelines also recommend the use of clofarabine for assertive therapy in suitable patients with either relapsed or refractory disease. For the drug to fulfil this function, it must be used together with granulocyte colony stimulating factor together with or without cytarabine. Idarubicin can be added to this regimen to facilitate the treatment process. (Ho *et al.*, 2015)

Various studies have been conducted with the aim of identifying the maximum tolerated dose for clofarabine. The original pediatric phase I study of the drug found a maximum tolerated dose (MTD) of 52 mg/m^2 per day. The same study identified dose-limiting toxicities of the drug as reversible hepatotoxicity as well as skin rash. The 2^{nd} phase of the study resulted in clofarabine being approved for relapsed pediatric ALL in 2004. Even so, the study did not confirm the activity of clofarabine on relapsed pediatric AML since the response rate was only 26% (van Eijkelenburg *et al.*, 2018). Only one-sided responses were obtained for relapsed pediatric AML, and this can potentially be attributed to the addition of patients that were heavily pretreated. On the contrary, a majority of early phase studies focused on adult AML revealed the antileukemic activity of clofarabine. Randomized data has also proven that clofarabine (20 mg/m^2 per day for 5 days) has no survival benefit over low dose cytarabine. Such an observation is at

the expense of the fact that remission rates got better among untreated older patients with AML and those with high-risk myelodysplastic syndrome (MDS). Another randomized study also compared cytarabine with clofarabine of 20 mg/m^2 per day for a period of 5 days. The dosage was administered through induction courses I and II among elderly AML. The study findings showed that the drug failed to show a survival benefit. Even so, more current research work by the HOVON-group demonstrated a survival benefit for patients randomized to clofarabine in AML sub-sets exposed to an intermediate risk. The dosage used in the study was 10mg/m^2 per day for a period of 5 days (van Eijkelenburg *et al.*, 2018).

Clofarabine combination therapy has also been developed to deal with the resistance associated with pediatric ALL. Such resistance could emanate from sequences with cyclophosphamide, etoposide and cyclophosphamide, or from topotecan, vinorelbine and thiopeta. Among children with either relapsed or refractory AML, a combination of clofarabine with cytarabine caused a 3-year pOS of 46%+-27% among the responders. The dosage for clofarabine was 52mg/m^2 per day for 5 days, while that of cytarabine was 1g/m^2 per day for 5 days. In another CLOUD study, the authors treated 9 children with either relapsed or refractory AML using a clofarabine dosage of 30mg/m2 per day for 5 days and liposomal daunorubicin of 60mg/m^2 for the 1^{st}, 3^{rd}, and 5^{th} days. 33% of the study participants attained complete remission (CR) and were transplanted subsequently (van Eijkelenburg *et al.*, 2018).

Chemotherapy based on clofarabine is also significant in the setting of refractory or relapsed acute myeloid leukemia. The sole curative treatment possibility for refractory or relapsed acute myeloid leukemia patients is the transplantation of allogenic hematopoietic stem cells. However, this can only be tried when the disease is in remission. Past research has shown that "salvage" therapy regiments tend to fail 30-50% of the time. Most of these regimens contain a high dose of cytarabine together with fludarabine or cladribine. The regime may or may not contain anthracyclines, mitoxantrone, or etoposide (Molteni *et al.*, 2017). One study reported the outcome of 14 patients that were treated with a clofarabine-based treatment that was implemented after at least one unsuccessful fludarabine-based "salvage" attempt in a "real life" context outside a clinical trial. The authors did not observe any death associated with the clofarabine-based treatment. 29% of the study sample attained complete remission, while only 7% attained a reduction of marrow blasts that were fewer than 10%. 3 out of the patients were transplanted successfully and showed the possibility for long-term survival. The study was limited in the sense that the study sample was ridiculously small and did not allow the authors to identify the clinical features that were obviously related to a promising outcome. Regardless of this limitation, the authors noted that all the three patients that displayed long-term survival were FLT3 wild type. In sum, the findings of the study indicate that "salvage therapy" based on clofarabine is suitable even after a fludarabine-based salvage attempt among patients with extremely poor expectancy. Even though, the success rate of this therapy is reported in an exceedingly small fraction of cases (3/14 or 21% of the study population) (Molteni *et al.*, 2017).

Another study by Chevallier and his colleagues prospectively examined the safety and effectiveness of a clofarabine, intravenous busulfan as well as antithymocyte globulin-based reduced-toxicity conditioning (CloB2A2) regimen. The authors carried out this procedure prior to allogenic stem cell transplantation.

The sample size of the study entailed 30 high-risk patients with a median age of 59 years. 11 of the patients had acute myeloid leukemia, 13 had severe lymphoblastic leukemia, 5 had myelodysplastic syndrome, while 1 had bi-phenotypic leukemia. These patients were included in the second phase of the study. During the period of the transplant, 20 patients were in the first complete remission, while 7 were in the second complete remission. 3 of the patients who had myelodysplastic syndrome were either reacting to chemotherapy or had not been treated previously. The CloB2A2 regiment was administered as follows: clofarabine of 30mg/m^2 per day for 4 days, busulfan of 3.2 mg/kg per day for 2 days, and antithymocyte globulin 2.5 mg/kg per day for a period of 2 days. The patients were followed up for a median period of 23 months. All the patients reported cases of engraftment. The general 1-year survival rate was 63+-9%, for leukemia-free survival was 57+-9%, for relapse incidence was 40+-9%, and for relapse incidence and non-relapse mortality rate was found to be 3.3+-3%. The authors also compared patients that had acute myeloid leukemia or rather myelodysplastic syndrome to those that were diagnosed with acute lymphoblastic leukemia or bi-phenotypic leukemia. The findings showed that the 1-year general survival rate was 75+-10% against 50+-13%, while leukemia-free survival rates were 69+-12% against 43+-13%. In the same way, the authors found that the 1-year relapse incidence was 25+-11% against 57+-14%.

Overall, these findings showed that the CloB2A2 regimen was feasible before allogeneic stem cell transplantation. This allowed for detailed engraftment as well as low toxicity. From the study, it was also clear that disease control was adequate, more so in patients with serious myeloid leukemia or the myelodysplastic syndrome (Chevallier *et al.*, 2014).

In a study by Eadon et al., the authors examined the genetic as well as the epigenetic variants that promote clofarabine cytotoxicity. In the study, the authors noted that the toxicity profile of clofarabine comprises of its expected bone marrow suppression. Moreover, the authors noted that the administration of clofarabine is related to transient transaminitis, infectious sequelae, and emesis. Eadon et al., also recognize that one other thing that is associated with the drug is severe acute kidney injury. This is of particular interest since clofarabine can contribute to renal filtration, reabsorption, and secretion with over 60% of the drug likely to be emitted in urine while unaffected. Many case reports as well as a number of phase II trials have shown rates of grade 3-4 renal toxicity in about 21% of the patients (Eadon *et al.*, 2013).

Clofarabine has compelling antileukemia activity and its addition in reduced-intensity conditioning (RIC) allogeneic hematopoietic stem cell transplantation (HSCT) for severe leukemia can possibly enhance the outcomes. In a research conducted by El-Jawahri et al., the authors implemented a phase II study, where busulfan of 0.8 mg/kg i.v. was administered two times each day on the 5^{th}, 4^{th}, 3^{rd}, and 2^{nd} days. They administered this drug together with clofarabine as a conditioning in dosages of 40mg/m2 i.v. each day on the 5^{th}, 4^{th}, 3^{rd}, and 2^{nd} days. The administration of the drugs was done before allogeneic 8/8 HLA matched the related or the unrelated HSCT. The key endpoint was donor neutrophil engraftment by the +40 day.

Some of the secondary endpoints identified in the study included the following: nonrelapse mortality (NRM), progression-free survival (PFS), severe graft-versus-host disease (GVHD), as well as overall survival (OS). The authors enrolled 34 patients for the study. Among these, 25 had severe myeloid leukemia, 5 had been diagnosed with myelodysplastic syndromes, while 4 had severe lymphoid leukemia. The authors achieved day 40+ engraftment with donor chimerism among 33 of 34 patients. One of the patients died prior to count recovery. The NRM for day 100 was 5.9% (95% confidence interval, 1.0 to 17.4), while that of 1-year was 24 % (95% confidence interval, 11 to 39). The authors found the relapse rate for 2 years to be 26% (95% confidence interval, 13 to 42). The cumulative incidences of severe and persistent GVHD were 21% and 44% in that order. The 2-year progression-free survival was 50% (95% confidence interval, 32-65), while the overall survival was 56% (95% confidence interval, 38-71). The 2-year progression-free survival and overall survival for patients that had AML in the first complete remission was 82% (95% confidence interval, 55-94). To summarize, the findings showed that reduced-intensity conditioning with busulfan and clofarabine leads to effective engraftment with appropriate rates of nonrelapse mortality and graft-versus-host disease (El-Jawahri *et al.*, 2016).

The eradication of the leukemic load is believed to be a requirement for successful treatment when dealing with refractory or relapsed acute myeloid leukemia (AML). Due to this fact, Loeffler and his colleagues examined toxicity as well as the anti-leukemic activity of a clofarabine-AraC salvage protocol prior to transplant. The authors carried out a retrospective analysis and observed the induction of objective remissions among 86% of the patients that were having clofarabine-AraC. This was in comparison to the 83% of the patients that had a subsequent high dose of AraC/mitoxantrone (S-HAM) as well as 50% after the mitoxantrone/ topotecane/AraC (MTC) salvage tactics.

The clofarabine used in the study conferred anti-leukemic activity to some of the patients who failed the earlier MTC or S-HAM therapy. The authors also recognized cytogenetically defined harmful risk markers to facilitate overall and leukemia-free survival. The findings of the study showed that clofarabine-AraC salvage tactic combined articulate anti-leukemic activity with the help of acceptable toxicity profile. The salvage strategy also allowed most of the patients with relapsed or refractory AML to go ahead to allo-SCT, even in high risk circumstances that were cytogenetically defined (Loeffler *et al.*, 2015).

CONCLUSION

Future investigations should be directed to assess the treatment outcome of Clofarabine based regimen as bridge for transplant in pediatric patients with refractory/relapsed leukemias. The objectives of the investigations should be concentrated on how management is conducted, transplant related toxicities and outcome of the transplant in terms of engraftment and infusion dependence in patients who received clofarabine based regimen. Additionally, it would be significant to evaluate the general and event free survival of pediatric patients.

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