

Influence of Hepatic Graft-Versus-Host-Disease (GVHD) on the Pharmacokinetics of Ciclosporin in a Case of Acute Myeloid Leukemia Treated at the EHU Oran

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Abstract:

Acute myeloid leukemia (AML) is a malignant blood disease that affects hematopoietic cells in the bone marrow. The best treatment for AML is allogeneic hematopoietic stem cell transplantation (HSC). To prevent and treat the main complication of allogeneic marrow transplant, graft versus host disease (GVHD), it is necessary to combine immunosuppressive therapy which includes ciclosporin (CsA).

The objective of our work is to study the influence of hepatic GVHD on the pharmacokinetics of ciclosporin in an AML case. This is an allografted patient (CSH), presented to our Pharmacovigilance department at the EHU of Oran in Algeria, with the aim of carrying out therapeutic pharmacological monitoring (TPM) of ciclosporin. We proceeded to assay for residual ciclosporinaemia from D1 of the allogeneic transplant. The patient presented a fluctuation of the trough concentrations, the explanation of which was an onset of acute hepatic GVHD, confirmed by biopsy with an elevated hepatic function, which represents an incidence varying between 10 and 50% in patients receiving a transplant from a genotypical donor. Without forgetting the great inter-individual and intra-individual variability of the response to ciclosporin, the environmental and pathological factors and the numerous drug interactions which can be the cause of modification of the pharmacokinetics and the pharmacodynamics of this drug. In conclusion, the pharmacological monitoring of ciclosporin, which is the treatment of choice to prevent or treat GVHD, is mandatory due to its low therapeutic index and high inter- and intra-individual variability.

Key words: therapeutic pharmacological monitoring (tpm), graft-versus-host-disease (gvhd) ciclosporin (csa), acute myeloid leukemia (aml), allogeneic transplant (at).

Introduction:

Acute myeloid leukemia (AML) is defined as a clonal malignant proliferation of immature myeloid cells at an early stage of differentiation (blasts), responsible for a bone marrow failure syndrome and/or a tumor syndrome (1).

It is now clearly established that the best treatment for acute myeloid leukemia (AML) is allogeneic (healthy donor) HSC allogeneic transplantation (HLA identical donor in the family) (2). However, there is only a geno- identical family donor in about 25-30% of cases, so this treatment is unfortunately only available to a minority of patients. The goal of HSC transplantation is to provide the patient with healthy, immunocompetent hematopoietic tissue as well as cells necessary for the

correction of deficient cellular metabolism.

To prevent graft rejection and, more importantly, to prevent or treat Graft-Versus- Host-Disease (GVHD), the main complication of allogeneic marrow transplantation, which is a major cause of medical problems and death following allogeneic stem cell transplantation, it is imperative to combine a standard treatment including ciclosporin (CsA).

CsA is one of the so-called low therapeutic margin drugs, with significant adverse effects such as nephrotoxicity, arterial hypertension, hepatotoxicity, digestive and neurological disorders (particularly convulsions in children) as well as gingival hyperplasia and hypertrichosis. In addition, it presents a significant inter-individual pharmacokinetic (PK) variability. These characteristics make CsA an

eligible drug for therapeutic pharmacological monitoring (STP).

For therapeutic pharmacological monitoring of cyclosporin, blood sampling is performed just before the next dose: this concentration, called "residual concentration" (Cres), thus allows to adjust the dosage according to the desired target (3).

The aim of this article is to discuss the influence of hepatic GVHD on the pharmacokinetics of cyclosporin in a patient with AML.

Case report:

This is a 32-year-old female patient with no medical and family

history, admitted to the allograft unit, department of hematology EHU Oran for allogeneic hematopoietic stem cell transplantation from an HLA-identical donor as a treatment for AML which is suspected on the basis of clinical symptoms (Fatigue, infections and bleeding) and confirmed by a complete blood count and a bone marrow biopsy.

Allograft was performed on September 16, 2020 (D0), after treatment with myeloablative chemotherapy as a graft conditioning protocol including fludarabine-busulfan 12 mg/kg (FB4).

Cyclosporin was introduced on D-3 of the allograft, September 13, 2020, at a dosage of 80mg/24h by electric syringe perfusion (PSE), associated with a drug regimen that is shown in Table 1 :

Treatment	Dosage
Heparin sodium	5800 UI/24h (PSE)
Zovirax (Aciclovir)	300 mg 2x/d
Fungizone (Amphotericin B)	01 tbsp 4x/d
Ursolvan (ursodesoxycholic acid)	200 mg 3x/d
Vfend (voriconazole)	200 mg 2x/d
Tavanic (Levofloxacin)	500 mg/d
Orgametril (lynestrenol)	5 mg/d

Table 1: The drug assessment administered to the patient with the corresponding dosages

On day 1 of the allograft (17.09.2020), the first sample for the determination of residual ciclosporinemia was received at the pharmacovigilance department, pharmacokinetic unit of EHU Oran. The ranges of residual ciclosporin concentrations were set by the team

of the allograft unit, haematology department.

The results of residual ciclosporinemia are presented in (figure 1), according to the dosages administered.

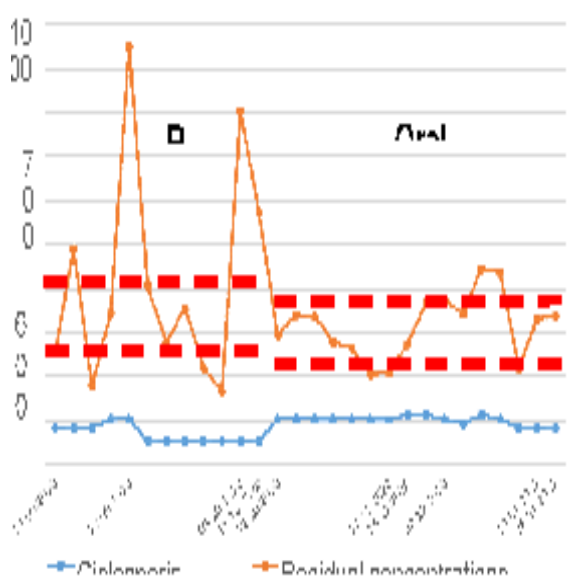


Figure 1: The evolution of residual ciclosporin concentrations according to the dosages administered as a function of time.

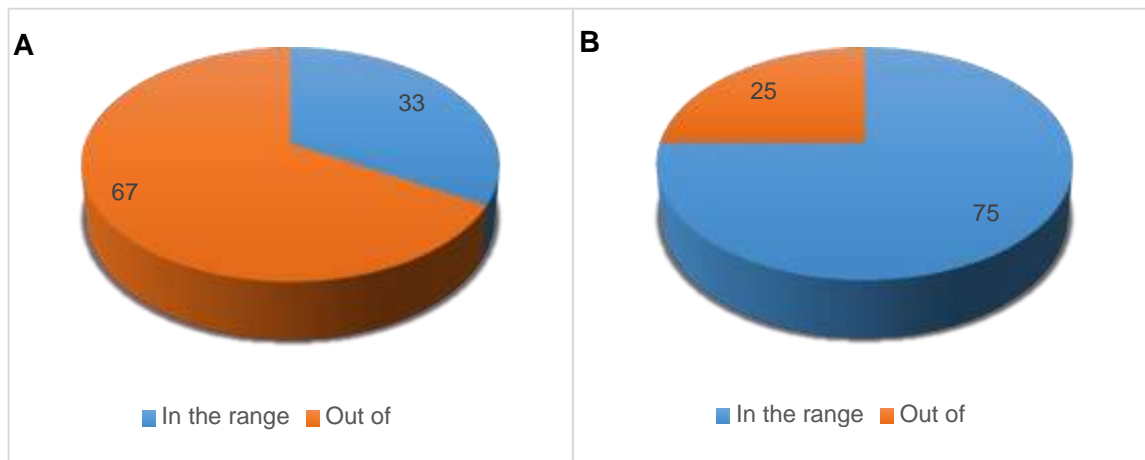


Figure 2: A: Percentage of residual cyclosporinemia administered by PSE within and outside the therapeutic range. B: Percentage of residual oral cyclosporinemia within and outside the therapeutic range.

Discussion:

Analysis of the case data led us to determine the following:

Overall the patient showed fluctuation in residual cyclosporin concentrations, especially in the period when the patient was on PSE, which lasted 24 days, of which 12 determinations were performed, of these 12 determinations, 67% (i.e. 8 determinations), the values were out of range (200-400 ng/mL) with 4 supra-therapeutic and 4 sub-therapeutic residual cyclosporinemia (figure 2: A).

This fluctuation, according to the referring allograft haematologist, is explained by the onset of acute hepatic GVHD at D12, confirmed by biopsy and an elevated hepatic work-up, with hyper-bilirubinemia associated with increased alkaline phosphatases and hepatic cytolysis.

GVHD is a frequent and serious complication of HSC allograft transplantation. The incidence varies according to studies from 10 to 50% in patients receiving a transplant from a geno- identical donor and up to more than 75% of patients transplanted with a pheno-identical donor according to different studies (4-5). This is an immune reaction involving the graft's T lymphocytes, which react against tissue antigens of the recipient that are not present in the donor (6-7).

This fluctuation can also be explained by the high inter- and intra-individual variability of the response to cyclosporine. The origin of this variability is partly genetic, for which it would be preferable to genetically stratify allograft recipients by identifying the CYP3A4 and ABCB1 gene. In addition, environmental and pathological factors or numerous drug interactions are likely to modify the pharmacokinetics and pharmacodynamics of this drug. This leads us to be very vigilant in the administration of cyclosporine by PSE and to undertake pharmacogenetic research including screening of genetic populations and ensuring population kinetics, in order to optimise dosing.

At D26 post-transplant, the patient emerged from bone marrow aplasia, which is defined as an absolute polynuclear neutrophil count (NNC)

≥ 0.5 G/L on two consecutive days (8-9). Thus cyclosporin was administered orally, where stabilisation of residual concentrations was observed over a period of 03 months, the patient had 16 determinations of which 75% (i.e. 12 determinations), the values were within the therapeutic range (Figure 2: B). A randomised trial in HSC allograft patients comparing PSE with oral cyclosporin after recovery from bone marrow aplasia showed improved stability of cyclosporinemia with

reduced side effects (10).

Balancing the immunosuppressive therapy, i.e. determining the optimal dose for the patient, is a prerequisite for its clinical stability. Oral administration requires regular dosing and very precise monitoring. Cyclosporin should be taken at fixed times in the morning and evening.

Conclusion:

Cyclosporin is the treatment of choice for the prevention of HSC transplant rejection and, more importantly, for the prevention or treatment of GVHD, the main life-threatening complication in allograft patients. The Pharmacological Therapeutic Follow-up of cyclosporin is mandatory in routine because of its low therapeutic index and potential drug interactions, as well as its high inter-individual and intra-individual variability to avoid a possible loss of health economy and an overcost knowing that allograft is very expensive and implies huge means.

The limitations of our study are summarised in the identification of CYP3A4 and ABCB1 genes for population stratification.

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