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Treatment of *FLT3*-mutated acute myeloid leukemia (AML) with midostaurin in Mexico: the challenges in a developing country.

Tratamiento con midostaurina de leucemia mieloide aguda con mutación en *FLT-3* en México: los retos en un país en desarrollo

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Abstract

BACKGROUND: The prognosis of acute myeloid leukemia (AML) is defined by cytogenetic and molecular assessment.

OBJECTIVE: To analyze the data of eight centers of Mexico treating patients with acute myeloid leukemia with the standard treatment of their institution plus midostaurin.

PATIENTS AND METHOD: A retrospective study was done with all the patients with newly diagnosed AML in eight centers who were assessed for *FLT3-ITD* and *TKD* mutations from September 2016 to September 2017 and treated with midostaurin if they had any *FLT3* mutation. We analyzed the data of eight centers in Mexico that treated AML patients with midostaurin and the standard treatment of their institution.

RESULTS: We assessed *FLT3* mutations in 79 patients with AML and found mutations in 11 (13.9%). We treated 7 AML-patients with chemotherapy and midostaurin: The CR rate was 100%. With a medium follow-up of 32.8 weeks, the overall survival and disease free survival were 71.4%. We reported adverse events associated with midostaurin in 57% of the total number of patients (4/7), all of them grade 1-2. In most cases the adverse effects were nausea and fatigue.

CONCLUSION: We have found, in concordance with previously reported data, that treatment with midostaurin is well tolerated and produces sustained responses. In developing countries we face for specific challenges for the diagnosis and treatment of AML.

KEYWORDS: Acute myeloid leukemia; Midostaurin.

Resumen

ANTECEDENTES: Hace poco se aprobaron para el tratamiento de la leucemia mieloide aguda terapias blanco dirigidas a mutaciones específicas.

OBJETIVO: Analizar los datos de ocho centros en México que trataron pacientes con leucemia mieloide aguda con el tratamiento estándar de su institución más midostaurina.

MATERIAL Y MÉTODO: Estudio retrospectivo en el que de septiembre de 2016 a septiembre de 2017 se incluyeron todos los pacientes con diagnóstico reciente de leucemia mieloide aguda en quienes se realizó la búsqueda de mutaciones en *FLT3*.

RESULTADOS: Se incluyeron 79 pacientes con leucemia mieloide aguda y se encontraron mutaciones en 11 (13.9%). Se trataron 7 pacientes con quimioterapia estándar y

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midosaturina. La tasa de remisión completa fue de 100%, con mediana de seguimiento de 32.8 semanas, la supervivencia global y libre de progresión fueron de 71.4%. Se reportaron eventos adversos asociados con midostaurina en 57% de los casos, todos ellos grado 1-2. Los eventos adversos más frecuentes fueron náusea y fatiga.

CONCLUSIONES: Encontramos, en concordancia con la información publicada, que el tratamiento con midostaurina es bien tolerado y efectivo. En países en desarrollo, el acceso a pruebas diagnósticas y a terapias novedosas son retos muy importantes para el diagnóstico y tratamiento de la leucemia mieloide aguda.

PALABRAS CLAVE: Leucemia mieloide aguda; midostaurina.

INTRODUCTION

The prognostic risk stratification in acute myeloid leukemia (AML) has dramatically changed in the last 20 years by the knowledge of the genetic and molecular landscape of AML. Nowadays, it is well recognized that genetic and molecular characteristics are the most relevant prognostic factors in AML.[1-4] The most recent European Leukemia Net (ELN) classification incorporates 6 different mutations to the classic karyotype to classify the patients between 3 prognostic categories.[5] In 2017, these advances in the knowledge of the disease biology were accompanied by the approval of 4 new drugs for AML; 2 of them are targeted therapies for specific mutations: Midostaurin for *FLT3* mutations and Evosidenib for *IDH2* mutations. Mutations on *FLT3* are one of the most common mutations, particularly in patients with normal karyotype, being present in 20-30% of AML patients (35% of patients with normal karyotype).[3,4,6] *FLT3* mutations are classified in two groups: internal tandem duplications (*FLT3-ITD*, 75-80%) and point mutations in the activating loop of the kinase domain (*FLT3-TKD*, 20-35%).[3,4,6] *FLT3-ITD* mutations have been consistently associated with high relapse-rate and worse overall survival (OS).[7,8] Several *FLT3* inhibitors have been developed in the last decade.[9] In 2017, midostaurin has been approved by FDA end EMA as the first *FLT3*-inhibitor, based on the advantages on disease free survival (DFS) and OS when combining midostaurin *vs.* placebo with standard induction and consolidation chemotherapy.[10]

In developing countries, we face some specific challenges. The molecular analysis is not widely extended, there is a lack of local standardized laboratories and the cost of a complete genetic and molecular assessment is sometimes prohibitive.

The objective of this paper is to report the experience of an AML Individual Patient Program in Mexico, with 7 patients treated with midostaurin and intensive chemotherapy.

MATERIAL AND METHOD

A retrospective study was done with all the patients with newly diagnosed AML in eight centers who were assessed for *FLT3-ITD* and *TKD* mutations from September 2016 to September 2017 and treated with midostaurin if they had any *FLT3* mutation. We included patients with newly diagnosed AML (WHO 2016,[11] excluding acute promyelocytic leukemia), older than 18 years, eligible for standard induction and consolidation chemotherapy, with *FLT3* mutations (both *ITD* and *TKD*), ECOG Performance Status of ≤ 3 and creatinine and direct bilirubin less than

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2.5 x ULN. Patients were excluded if they had completed the 2nd consolidation cycle, history of hypersensitivity to drugs or metabolites similar to midostaurin, LVEF < 45% (by echocardiogram or MUGA) or symptomatic heart failure, any uncontrolled disease or QTc > 470 msec.

Patients were treated according to their institution´s standard treatment. Midostaurin was added to the treatment as soon as it was available: 50 mg twice daily on days 8 to 21 of each induction or consolidation cycles and 50 mg twice daily continuously for one year as maintenance. The response criteria were those recommended by the European Leukemia Net.[5] The cytogenetic and molecular risk were established according to the NCCN recommendations.[12]

Statistical analysis was recorded in a database, post processed arithmetically with Microcal Origin 7.0 and then in SPSS version 17.0.1 for Windows. Descriptive statistics were performed over the time registration, overall survival, time for remission/relapse median analysis and standard deviation evaluated over uncontrolled-longitudinal analysis criteria of the population.

RESULTS

Between November 2016 and September 2017, 79 patients were assessed for *FLT3* mutations in these centers. We found *FLT3* mutations in 11 patients (13.9%) and 7 patients met the inclusion criteria. The main characteristics of these patients are shown in **Table 1**. The mean age was 57.7 years (40-75 years). Almost all of them had a high white blood cell count (6/7) with a range of 3.2-220 x10^9/L. Most patients (except two) had a normal karyotype. All the *FLT3* mutations were *FLT3-ITD*. Six patients were considered high risk according the NCCN classification. A patient with a Core Binding Factor (CBF)–AML (Inv (16)) had also a *KIT* mutation and was considered to be intermediate risk. The *NPM*1 mutations tests were performed in 2 patients only (patients 3 and 7) and were positive in one of them (patient 7). In only one case, an extended molecular analysis was made, being the CBF-AML patient in whom *FLT3-ITD/KIT* mutations were found. The most used induction regimen in 5 patients was 7+3, with different anthracyclines ((2) daunorubicin, (2) idarubicin and 1 with epirubicin). **Table 2**.

All the patients were evaluable for response: 6/7 obtained complete remission (CR) with first

Table 1. Patient characteristics

Patient ID	Age	Gender	WBC at diagnosis (x 10^9/L)	WHO classification	Karyotype	Cytogenetic /molecular risk
1	41	Female	37.90	AML NOS	Normal	High
2	66	Female	50.00	AML NOS	Normal	High
3	47	Male	18.00	AML with recurrent genetic abnormalities	46 XY (inv16),t(9;10) /KIT mutation	Intermediate
4	73	Female	125.00	AML with myelodysplasia-related changes	Normal	High
5	48	Female	32.00	AML with myelodysplasia-related changes	del(11)(q23)	High
6	66	Female	3.2	AML with myelodysplasia-related changes	Normal	High
7	62	Female	222.00	AML NOS	Normal	High

NOS: not otherwise specified; AML: acute myeloid leukemia.

induction chemotherapy and 1/7 with a second cycle of induction chemotherapy. The CR rate was 100%.

Most of the patients (6/7) receive consolidation with high-dose cytarabine (one of them under FLAG regimen). None of the patients were considered for allogeneic transplantation of hematopoietic progenitor cells.

With a median follow-up of 32.8 weeks, the overall survival and disease free survival are 71.4%. Two (28.57%) patients died in CR because of infections: one of them during consolidation and one patient in maintenance. The remaining patients (5/7) are alive and in CR (**Table 2**).

Midostaurin treatment started at different times, in the majority of patients in the second consolidation phase, only in two cases midostaurin started since the induction (**Table 2**).

We reported midostaurin related adverse events in 57% of the patients, all of them grade 1-2. In most cases the adverse effects were nausea and fatigue. There was one case of digestive tract bleeding, possibly associated with midostaurin that required temporary suspension of the drug. Only one patient required dose adjustment because of concomitant use of posaconazole. During the assessed period, no disease relapse was observed in all patients.

Table 2. Treatment and outcomes

Patient ID	Chemotherapy regimen	Midostaurin start at	Midostaurin dose adjustment	Midostaurin associated adverse events	Actual status/ weeks in remission
1	7+3 (epirubicin) 3 consolidations with HDAC	Consolidation 2	No	g1-2	Maintenance 23.6 weeks
2	7+3 (daunorrubicin) 2 consolidations with HDAC	Induction	No	g1-2	Maintenance 33.96 weeks
3	FLAG-Ida 4 consolidations with FLAG	Consolidation 2	Yes	g1-2	Maintenance 13.48 weeks
4	7+3 (idarubicin) 3 consolidations with low dose Ara-C	Consolidation 1	No	No	Died in CR during consolidation (pneumonia) 11.4 weeks
5	7+3 (idarubicin) 3 consolidations with HDAC	Consolidation 2	No	g1-2	Died in CR in maintenance (infection) 32.8 weeks
6	Ara-C / MTX Re-induction with 7+3 3 consolidations with HDAC	Consolidation 2	No	No	Maintenance 30 weeks
7	7+3 (idarubicin) 3 consolidations with HDAC	Induction	No	No	Consolidation 11.4 weeks

HDAC: high dose cytarabine; Ara-C: cytarabine; CR: complete remission; Ara-C /MTX: high dose cytarabine and mitoxantrone.

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DISCUSSION

In this case series of *FLT3*-mutated AML patients, on basis on the NCCN proposed classification we classified all the patients, being 6/7 of high risk and 1/7 of intermediate risk.[12] It is worth mentioning, that the current ELN recommendations include the most relevant mutations measurement to establish the prognosis: *NPM1, CEBPA, RUNX1, FLT3, TP53* and *ASXL1*.[5] Additionally, they recommend the measure of allelic load of *FLT3* mutation to define the risk category. Both the *FLT3* allelic load, and the interaction of this mutation with *NPM1* mutations, have demonstrated to influence the prognosis of *FLT3-ITD* mutations.[13-15] Therefore, in our patients with normal karyotype and *FLT3-ITD* mutations, considered as unfavorable risk, if the allelic load was low (< 0.5) or even high, but associated with mutations in the *NPM1* (as is the case of the Patient 7), according to the ELN, would be considered as intermediate risk. This is an important challenge for developing countries where we have mutational tests access difficulties.

On the other hand we have one patient with Inv(16) whom according to the general classifications is considered on favorable risk; however the *KIT* mutation gives him an adverse risk. The adverse risk of *KIT* mutations in core binding factor (CBF) leukemia is much clearer in those associated with t(8;21) than those associated with Inv(16).[16-18] The prognostic impact of *FLT3* mutations in CBF leukemia is even less clear yet.[19,20] The co-existence of mutations in *FLT3-ITD* and *KIT* is not common in CBF leukemia. An analysis of the German-Austrian AML Study Group found this coexistence in 6% of the CBF leukemia and also found that the *KIT* was associated with lower relapse free survival and *FLT3* to lower overall survival; interestingly the *FLT3-TKD* and not *FLT3-ITD* mutation.[21] All these data suggest that these mutations confer a worse prognosis for this leukemia with Inv(16). However, it should be mentioned that in an MD Anderson study of CFB leukemia patients treated with FLAG + gemtuzumab ozogamicin in first line, mutations in *FLT3* and in *KIT* did not have a prognostic impact.[22]

On the other hand, in the RATIFY study, midostaurin in addition to standard chemotherapy has demonstrated to improve the prognosis of these patients, improving event-free survival and overall survival.[10] Only 5.3% of the patients had CBF leukemia and we don´t know if in this subgroup of patients the benefit of midostaurin is conserved. However, given the potential adverse prognosis of *FLT3* and *KIT* mutations, we assume that is reasonable to add midostaurin to the treatment of this patient.

Despite being a group of high-risk patients: 4/7 over 60 years, 42.8 % associated with myelodysplasia and 6/7 of high cytogenetic/molecular risk; although still short term follow-up, there have been no relapses or deaths from progression. Two patients died, due to infections: a 73-year-old woman with pneumonia during consolidation and a 48-year-old woman during maintenance. This demonstrates how supportive care, especially in older patients, is fundamental.

Despite being a small number of cases, it highlights some challenges that we face for the treatment of AML in Mexico. First, the knowledge of the genetic and molecular characteristics of AML has allowed a precise risk classification and the use of target therapies. In addition to karyotype and the 6 mutations recommended by the ELN, IDH1-2 mutations are becoming very necessary because of the potential use if IDH-inhibitors. The use of next-generations sequencing (NGS) panels of the individual assessment for each mutation, makes the diagnostic approach of AML very expensive. In Mexico, it is estimated that only the 8.8% of the population has some private medical insurance system.[23] The costs of

a broad panel of molecular tests can hardly be covered by national health systems. If the costs of potential target therapies are added, financial toxicity makes them prohibitive in the Mexican context. We need group as a medical community to make this diagnostic test affordable.

CONCLUSIONS

In developing countries, we face specific challenges for the management of adult patients with AML. We have found, in concordance with previously reported data, that treatment with midostaurin is well tolerated and produces sustained responses in patients with AML.

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