V JORNADA ONCOFARMA

Actualización en el manejo de la Leucemia Mieloide Aguda en el paciente adulto y pediátrico

GEDEFO Centro - Canarias y Cataluña - Baleares

Manejo de la toxicidad y atención farmacéutica en los tratamientos de recaída y enfermedad refractaria

ORGANIZA:

sefh Sociedad Española de Farmacia Hospitalaria

fefh Fundación Española de Farmacia Hospitalaria

gedefo Grupo de Farmacia Oncológica de la sefh

Gema Casado Abad
F.E.A. Sº Farmacia.
Hospital Universitario La Paz

CASO CLÍNICO 2:

10/12/20

- ✓ Mujer 55 años.
- ✓ LMA de alto riesgo citogenético (cariotipo complejo) y FLT3 -TKD mutado.
- ✓ 7/11/20: Recibió tto de inducción - esquema 3x7+ midostaurina:

Idarrubicina 12 mg/m^2 i.v. días 1 al 3 + citarabina 200 mg/m^2 i.v. días 1 al 7 + midostaurina 50 mg/12 h. v.o. días 8 al 21

- ✓ Médula + 14: 60% blastos, otra nueva monosomía 15.
  Fin de tratamiento: 60% blastos.
- ✓ Refractaria a tratamiento de inducción. Traslado a HULP. Para tto rescate y posterior aloTPH (hermana HLA idéntico).

10/12/20

- ✓ Analítica ingreso: Hb 9,9 g/dl ; Hto 29,3% **; Blastos 53%** Plaquetas 27.000/µl

- ✓ Pretende inclusión de E.C.: ***Protocol ARO-013***

Phase III Randomized, Double-blind, Placebo-controlled Study Investigating the Efficacy of the Addition of ***Crenolanib*** *to Salvage Chemotherapy Versus Salvage Chemotherapy Alone in Subjects ≤ 75 Years of Age with Relapsed/Refractory FLT3 Mutated Acute Myeloid Leukemia.*

- ✓ No cumple criterios de inclusión:
estudio NGS: no se detecta FLT3. Se descarta tto.

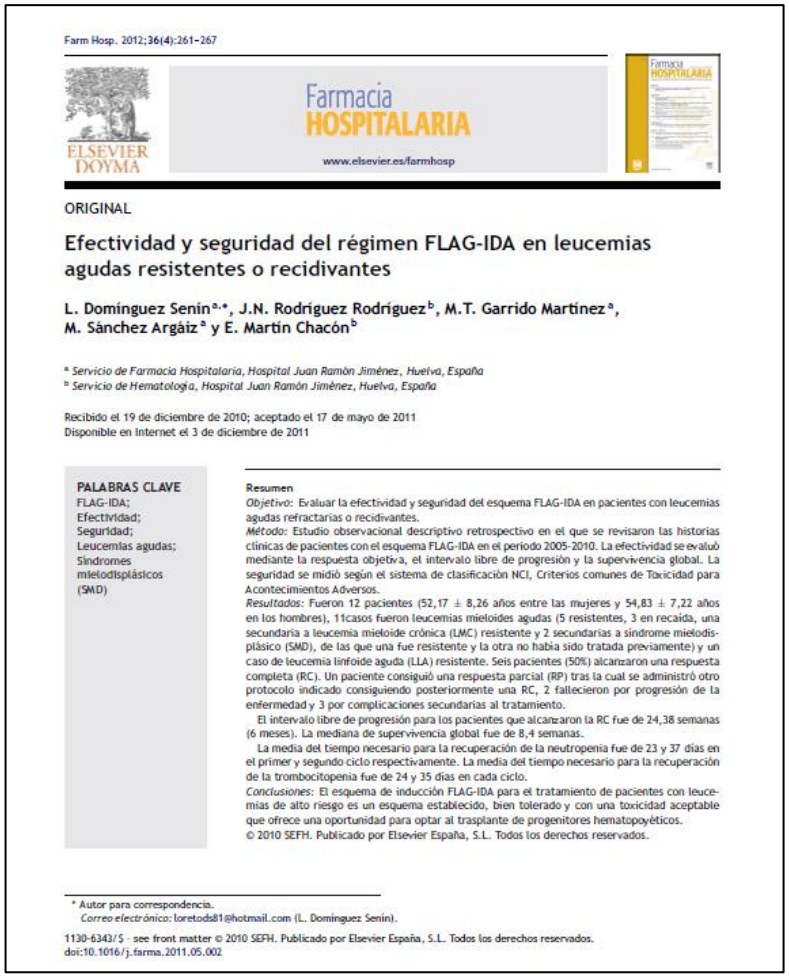
- ✓ Colocación CVC: Hickman

13/12/20

- ✓ Pico febril: cefepime 2g/8 h y vancomicina 1g/12 h

15/12/20

✓ Tratamiento de rescate con FLAG-IDA:



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ORIGINAL

Efectividad y seguridad del régimen FLAG-IDA en leucemias agudas resistentes o recidivantes

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PALABRAS CLAVE
FLAG-IDA;
Efectividad;
Seguridad;
Leucemias agudas;
Síndromes mielodisplásicos (SMD)

Resumen
Objetivo: Evaluar la efectividad y seguridad del esquema FLAG-IDA en pacientes con leucemias agudas refractarias o recidivantes.
Método: Estudio observacional descriptivo retrospectivo en el que se revisaron las historias clínicas de pacientes con el esquema FLAG-IDA en el período 2005-2010. La efectividad se evaluó mediante la respuesta objetiva, el intervalo libre de progresión y la supervivencia global. La seguridad se midió según el sistema de clasificación NCI, Criterios comunes de Toxicidad para Acontecimientos Adversos.
Resultados: Fueron 12 pacientes (52,17 ± 8,26 años entre las mujeres y 54,83 ± 7,22 años en los hombres), 11casos fueron leucemias mieloides agudas (5 resistentes, 3 en recaída, una secundaria a leucemia mieloide crónica (LMC) resistente y 2 secundarias a síndrome mielodisplásico (SMD), de las que una fue resistente y la otra no había sido tratada previamente) y un caso de leucemia linfoide aguda (LLA) resistente. Seis pacientes (50%) alcanzaron una respuesta completa (RC). Un paciente consiguió una respuesta parcial (RP) tras la cual se administró otro protocolo indicado consiguiendo posteriormente una RC, 2 fallecieron por progresión de la enfermedad y 3 por complicaciones secundarias al tratamiento.
El intervalo libre de progresión para los pacientes que alcanzaron la RC fue de 24,38 semanas (6 meses). La mediana de supervivencia global fue de 8,4 semanas.
La media del tiempo necesario para la recuperación de la neutropenia fue de 23 y 37 días en el primer y segundo ciclo respectivamente. La media del tiempo necesario para la recuperación de la trombocitopenia fue de 24 y 35 días en cada ciclo.
Conclusiones: El esquema de inducción FLAG-IDA para el tratamiento de pacientes con leucemias de alto riesgo es un esquema establecido, bien tolerado y con una toxicidad aceptable que ofrece una oportunidad para optar al trasplante de progenitores hematopoyéticos.

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ORIGINAL ARTICLE

D. Pastore · G. Specchia · P. Carluccio · A. Liso · A. Mestice · R. Rizzi · G. Greco · C. Buquicchio · V. Liso

FLAG-IDA in the treatment of refractory/relapsed acute myeloid leukemia: single-center experience

Received: 22 November 2002 / Accepted: 23 January 2003 / Published online: 15 March 2003

Abstract We evaluated the efficacy and toxicity profiles of the combination of fludarabine, high-dose cytosine arabinoside (AraC), idarubicin, and granulocyte colony-stimulating factor (G-CSF) in refractory/relapsed acute myeloblastic leukemia (AML) patients. Between October 1998 and February 2002, 46 AML patients were treated with FLAG-IDA (fludarabine 30 mg/m², AraC 2 g/m² for 5 days, idarubicin 10 mg/m² for 3 days, and G-CSF 5 μg/kg from day +6 until neutrophil recovery). Thirty patients were in relapse after conventional chemotherapy including cytarabine, etoposide, and daunorubicin or mitoxantrone according to the GIMEMA protocols. Four were in relapse after autologous peripheral stem cell transplantation and two after allogeneic bone marrow transplantation. Ten patients had refractory disease (after 10 days of standard doses of cytarabine, 3 days of mitoxantrone or daunorubicin, and 5 days of etoposide). Recovery of neutrophils and platelets required a median of 19 and 22 days from the start of therapy. Complete remission (CR) was obtained in 24 of 46 patients (52.1%) and 3 of 46 (6.6%) died during reinduction therapy: 2 due to cerebral hemorrhage and 1 due to hyperpyrexia (Candida tropicalis). Fever >38.5°C was observed in 40 of 46 patients (86.9%), 27 had fever of unknown origin (FUO) and 13 documented infections; 31 of 46 (67.3%) developed mucositis and 14 of 46 (30.4%) had grade 2 WHO transient liver toxicity. After achieving CR, 11 patients received allogeneic stem cell transplantation, 4 patients received autologous stem cell transplantation, 4 were judged unable to receive any further therapy, and 5 refused other therapy. Ten patients are at present in continuous CR after a median follow-up of 13 months (range 4–24). In our experience, FLAG-IDA is a well-tolerated and effective regimen in relapsed/refractory AML. The toxicity is acceptable, enabling most patients to receive further treatment, including transplantation procedures.

Keywords Acute myeloid leukemia · Refractory · Relapsed · FLAG-IDA

Introduction

About 50–80% of adult patients with de novo acute myeloblastic leukemia (AML) achieve complete remission (CR) with the currently available chemotherapy regimen consisting of anthracyclines and cytarabine [4, 29, 30]. However, 15–25% of patients fail to achieve CR because of resistance to treatment and 40% of CR patients will relapse within 2 years. Although several different chemotherapy combinations have been administered to patients with refractory/relapsed AML, the prognosis in this subset of patients is still poor, with a CR rate ranging from 30 to 40% [2, 10, 14, 16, 18, 26]. The goal of reinduction chemotherapy varies from achievement of long-term and complete remission (CR) to providing a bridge to hemopoietic stem cell transplantation (HSCT) aimed at prolonged disease-free (DFS) and overall survival (OS) or to temporary prolongation of life and palliation of symptoms. Most patients have already been exposed to intensive multiagent chemotherapy, and most reinduction regimens in current use cause substantial toxicity [7, 20, 27]. High- or intermediate-dose cytarabine (AraC) has been reported to be effective in the salvage treatment of AML [2, 5, 10, 17, 18]. Addition of the purine nucleoside analogue fludarabine to AraC increases the rate of accumulation of AraCTP in leukemic blasts by a median one- to sevenfold in in vitro studies [12]. The clinical efficacy of this approach depends on the higher intracellular concentration of the active metabolite Ara-C-5′-triphosphate (AraCTP) and the combination of flu-

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15/12/20

✓ Tratamiento de rescate con FLAG-IDA:

✓ Fludarabina 30 mg/m^2 i.v. días 1-4 (30 min.) + citarabina 2000 mg/m^2 días 1-5 (4 h.) + Idarrubicina 12 mg/m^2 días 1-3 (15 min.).

Administrar citarabina: 4 h. después de comenzar infusión de fludarabina.

✓ Tto de soporte:

G-SCF 300 µg s.c. : 5 días.

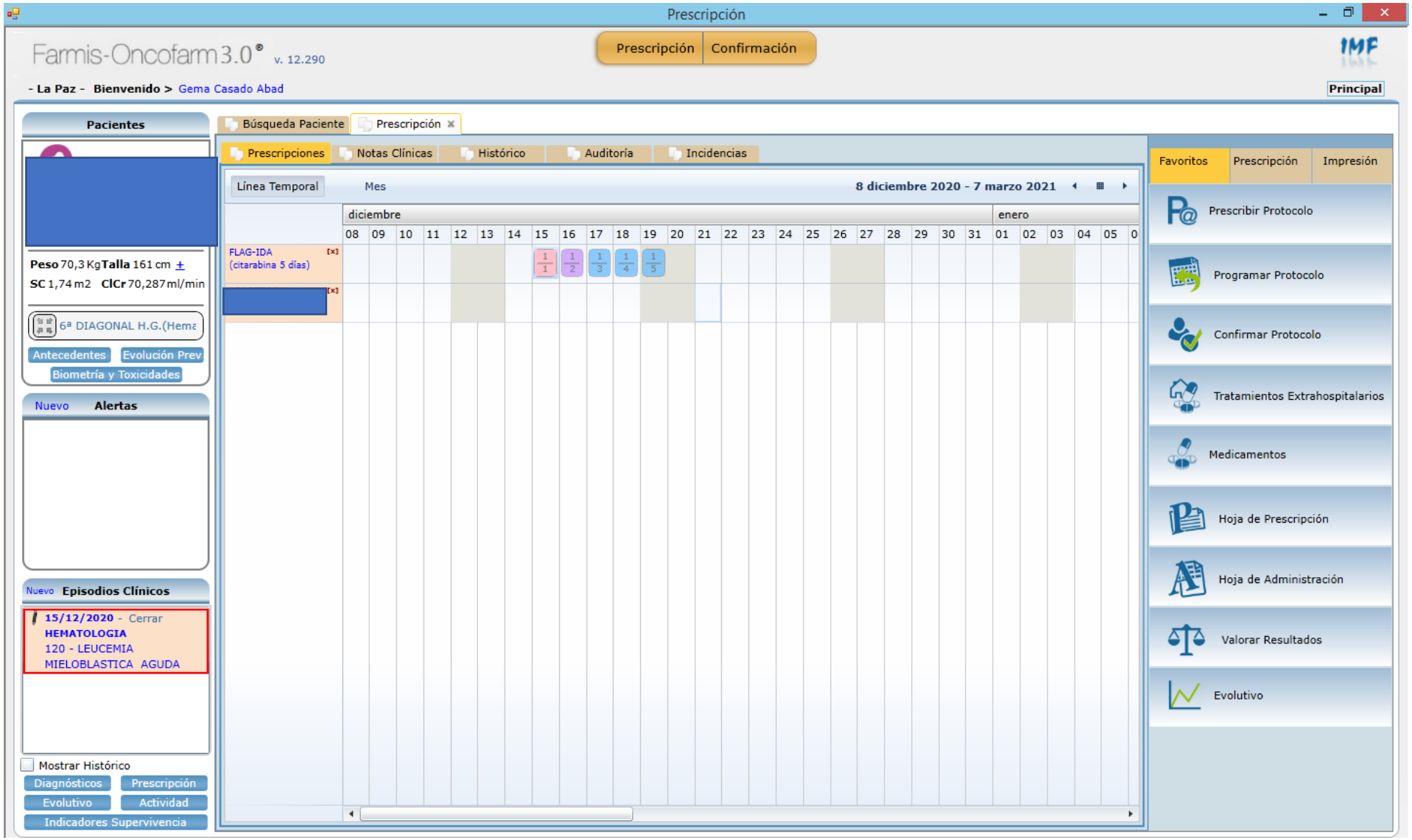
Hidratación y alcalinización. Alopurinol 300 mg comp. /día.

Medidas especiales administración de citarabina:

lagrimas artificiales y colirio de dexametasona (2 gotas en cada ojo cada 6 horas).

vitamina B6 ampolla, antes de cada dosis de citarabina.

cotrimoxazol+ ácido fólico (L.X.V).



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WEBINAR V JORNADA ONCOFARMA

Actualización en el manejo de la Leucemia Mieloide Aguda en el paciente adulto y pediátrico

GEDEFO Centro - Canarias y Cataluña - Baleares

15/12/20

- ✓ Tener en cuenta:

Toxicidad hematológica: anemia, trombocitopenia y neutropenia.

Toxicidad cardiaca: antraciclinas. Solicita electrocardiograma.

16/12/20

- ✓ Persistencia de fiebre y aumento de RFA. Oxigenoterapia.
- ✓ Aciclovir 800 mg 1comp/12 h.
- ✓ Meropenem 1g/8h. vancomicina 1g/8h.
- ✓ Posaconazol 300 mg/día v.o. (guías ECIL3, grado A1).

- ✓ Rash abdominal: citarabina. Pauta betametasona crema.

17/12/20

- ✓ Traslado a UCI: Shock séptico de origen respiratorio (posible LII) vs tunelitis CVC.

- ✓ Meropenem 2g/8h. y linezolid 600 mg iv/12 h. .
- ✓ Levofloxacino 500 mg iv/12 h.
- ✓ Anfotericina B 200 mg/24 h. + cotrimoxazol 2 amp/6h + corticoide
- ✓ Aciclovir 670 mg/ 8h IV.

- ✓ Retira CVC por sospecha de infección.
- ✓ Buena evolución clínica y no se obtienen cultivos microbiológicos.
- ✓ Traslado a planta: evoluciona favorablemente.

20/12/20

28/12/20

- ✓ Retira progresivamente terapia antimicrobiana: afebril.
- ✓ Retira oxigenoterapia.
- ✓ Colocación CVC tipo Hickman.

30/12/20

- ✓ Nuevo episodio desaturación que requiere aporte de oxígeno.
- ✓ Inicio de antibioterapia con meropenem 1g/8h. cotrimoxazol 2 ampollas/ 4h.
- ✓ Aciclovir 1000 mg/ 24 iv. Levofloxacino 500 mg iv/día.
- ✓ Posaconazol 300mg iv/24 h.

- ✓ 48 h: aislamiento de S. epidermis en hemocultivos.
- ✓ Añade tto vancomicina y sellado catéter con vancomicina intraluminal

HOSPITAL UNIVERSITARIO LA PAZ Guía de elaboración y control

7 Solución estéril intracatéter - VANCOMICINA 5 MG/ML SELLADO CATETER [Cantidad: 20] NºForm

Lote Núm.int. Localiz

Vancomicina		0,025	g	**[0,5]**
Cloruro sódico 0,9%	csp	5	ml	**[100]**
Vial/5 mL		1	u.	**[20]**

F.Recep.: 08-02-2021 F.Elab.: 08-02-2021
Caducidad: 15-02-2021 Núm.Ped.: 364
Núm.Rec.: 12430
Paciente: STOCK

Modus Operandi:

PREPARACIÓN EN CFL VERTICAL.
1.- Reconstituir un vial de Vancomicina 500 mg iv ® con 10 ml de agua para inyección.
2.- Extraer 10 ml de una bolsa de Cloruro Sódico 0,9% 100 ml.
Añadir 10 ml del vial de Vancomicina 500mg ya reconstituido al Cloruro Sódico 0,9% para obtener una concentración de 5 mg/ml.
3.- Dosificar los viales estériles necesarios por cada paciente con 5 ml de solución de Vancomicina 5 mg/ml empleando un filtro de 0,2 µ.
4.- Etiquetar cada vial
5.- Dejar en nevera la bolsa de Vancomicina 5mg/ml hasta caducidad.

OBSERVACIONES: Además de lote y caducidad, anotar nombre comercial de vancomicina.

Utillaje:
Jeringas, trasvasador, filtro esterilizante 0,22 micras y agujas

Control analítico:

Control de calidad:

Solución transparente sin partículas en suspensión.

Material de acondicionamiento:
20 VIALES VIDRIO ESTÉRILES 10 ML

Caducidad: 15-02-2021

Conservación: En frigorífico (2-8ºC).

Notas:

-Observaciones:
- Vancomicina 5 mg/ml es una "solución madre", caducidad 7 días.
- La Guía de elaboración es válida esa semana. Los viales se reetiquetan por paciente y se pega una etiqueta en la Guía
- Salida a la unidad con mayor consumo semanal

Recepcionado por: Fátima Ros Castellar **Elaborado por:** Laura Sanz Baro

Firmado:

- ✓ Buena evolución clínica de forma progresiva, permite desescalar antibiótico.

5/01/21

- ✓ Niveles de vancomicina: 29,57 µg/ml (15-20 µg/ml). Suspende y se ajustan niveles 6/01/21.

7/01/21

- ✓ Hemocultivos de control de sellado a 5 días: aislamiento de S. epidermis. Paciente afebril.

15/01/2021

- ✓ Pico febril y retirada de CVC.
- ✓ Rx torax: neumonía en LSD.
- ✓ Meropenem y Linezolid.
- ✓ Aciclovir y Posaconazol profilaxis.

18/01/21

✓ +36 FLAGIDA: repite AMO 20% blastos.

22/1/21

✓ Refractariedad: tto de rescate con azacitidina + venetoclax

TIMING DEL ALO-TIR SECUENCIAL (Figura 1):

- En situación de químio-resistencia a la inducción (2 ciclos, uno con Ara-C 2g/m2)
- ERM persistente o recaída post tratamiento Venetoclax-AZA o HMA, en pacientes "fit"
- Otras recaídas con baja % de blastos en MO <25%

1. LMA Refractaria: persistencia de > 5% blastos o EMR + tras 2 ciclos QT inducción que incluya Citarabina a altas dosis (HDAC), en ausencia de un ensayo clínico abierto: plantear rescate con Venetoclax-AZA por uso compasivo. Intentar realizar el TPH en los primeros 3 meses.

   a) Si RC, EMR -, paciente fit: AloTPH mieloablativo.
   b) Si no RC con bajo % blastos en MO < 25% o EMR+ pre-trasplante: realizarían un Alo-TIR Secuencial (con Bu x 2 ó 3 días, según edad y Sorror HCT-CI), seguido de intervenciones profilácticas post-trasplante combinando estrategias farmacológicas con ILD: Hipometilantes (HMA), inhibidores de dianas moleculares (Sorafenib, Gilteritinib, Evosidenib, Idasidenib, etc) o Venetoclax en combinación con HMA (por uso compasivo o si según disponibilidad de un ensayo clínico en este escenario del post-trasplante)

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The highs and lows of venetoclax with hypomethylating agents for refractory AML

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ARTICLE INFO

Keywords:
Acute myeloid leukemia
Venetoclax
Azacitidine
Decitabine

Treatment of acute myeloid leukemia (AML) has changed dramatically over the last several years, as novel chemotherapeutics are incorporated into standard therapy. At the time of AML diagnosis, patients and physicians now confront a far more complex treatment decision tree, which may also impact future options in the case of relapsed or refractory disease. At the same time, the approach to AML progression now takes into account new molecular targets of treatment, the potential to bridge even older patients to a transplant, and a growing number of effective novel therapies.

Until only a few years ago, relapsed or refractory AML (R/R AML) left providers and patients deciding between two general extremes: intensive chemotherapy using a reinduction regimen incorporating traditional cytotoxic agents; or using a palliative treatment – commonly one of the azanucleosides, azacitidine or decitabine (hypomethylating agent therapies, "HMA"). The former provided a moderate chance of attaining a remission, but often with significant toxicity; in contrast, the response rate to HMA monotherapy is quite low, although the immediate toxicities from treatment may be perceived as more manageable [1]. Since then, the use of targeted agents as salvage therapy has become an appealing option, such as for mutations in the *IDH1* or *IDH2* genes or mutation in the FLT3 receptor, but such alterations are only present in a minority of AML cases.

In contrast, adding venetoclax to standard HMA chemotherapy does not explicitly depend upon the presence or absence of a particular mutation. This has some benefits for venetoclax + HMA as a treatment strategy: there is no delay in waiting for the results of next-generation sequencing, and molecular targets may be preserved as future salvage options, if needed. The response rates of patients with newly-diagnosed AML who are then treated with venetoclax in combination with HMA are encouraging, and although not directly compared to date, may rival the response rates seen with standard frontline induction regimens – with over 60 % reporting CR or CRi [2,3]. These and other studies have resulted in the uptake of HMA + venetoclax in clinical practice. An outstanding question, however, is whether the activity of this combination is preserved and toxicity acceptable when used as salvage for relapsed or refractory disease.

Many questions then arise with HMA + venetoclax for relapsed or refractory AML: who is likely to respond, what is the optimal dosing, should this be prioritized over other options for refractory disease – including oral targeted therapies. To date, there is limited data for HMA + venetoclax in R/R AML available to inform clinical practice. DiNardo and colleagues retrospectively identified patients treated with venetoclax combinations, primarily with HMA or low-dose cytarabine (LDAC), and reported a far more modest response rate in the R/R setting of only 9 patients of 43 (21 %, 2 CR, 3 CRi, and 4 morphologic leukemia-free state) [2]. As may be expected, complications seen in R/R AML were more frequent than in the front-line setting, with 72 % having a grade 3 or higher infection, and 5 early deaths within 30 days (12 %). A separate retrospective analysis by Aldoss and colleagues, in contrast, showed more encouraging response rates in the salvage setting [4]. In that study, a total of 33 patients were treated with HMA + venetoclax, with a CR + CRi rate of 51 % (17 of 33, 10 CR, 7 CRi); nearly all responses occurred within three cycles of treatment, and just over half of patients experienced an SAE during the first treatment cycle.

In the current paper, Gaut and colleagues describe 14 patients with relapsed or refractory AML who were treated with venetoclax combined with either HMA or low-dose cytarabine [5]. This series reports an overall response rate of 35.7 % - three patients with CRi and two

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Research paper

Venetoclax combination therapy in relapsed/refractory acute myeloid leukemia: A single institution experience

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ARTICLE INFO

Keywords:
Acute myeloid leukemia
Relapsed/refractory
Venetoclax
Objective response rate
Progression-free survival

ABSTRACT

Venetoclax (VEN) is a selective BCL-2 inhibitor that has been shown to be effective when used in combination with hypomethylating agents (HMAs) or low-dose cytarabine (LDAC) for treatment-naïve, elderly acute myeloid leukemia (AML) patients unfit for intensive chemotherapy. Data on its use in the relapsed/refractory setting are limited. A retrospective analysis was performed among 14 patients with relapsed or refractory AML treated with VEN combination therapy at the University of California Los Angeles from 2018-2019. Eight patients received VEN in combination with azacitidine, 5 patients with decitabine, and 1 patient with LDAC. The majority (10 patients, 71.4%) had adverse cytogenetics. Three patients (21.4%) had undergone an allogeneic stem cell transplant prior to VEN therapy, and 5 patients (35.7%) had leukemia that failed HMA therapy prior. The objective response rate (ORR) was 35.7% (3 patients achieved complete remission with incomplete hematologic recovery and 2 patients achieved partial remission). Three patients (21.4%) were successfully transitioned to either allogeneic bone marrow transplant (2 patients) or donor lymphocyte infusion (1 patient). Seven patients (50.0%) developed a grade 3 or greater infection following VEN therapy, and 3 patients (21.4%) developed a grade 3 or greater intracranial hemorrhage. Three patients experienced early death within 30 days of therapy (2 from infection, 1 from bleeding). The median overall survival (OS) was 4.7 months, and the 1-year OS rate was 23.6% (95% CI 4.4–51.2) for the entire patient cohort. Overall, the response rate was not inferior to that with conventional salvage chemotherapy, but there were notable complications as a result of prolonged cytopenias.

1. Introduction

Venetoclax (VEN) is a highly selective inhibitor of the antiapoptotic protein B-cell lymphoma 2 (BCL-2) that can restart the deregulated process of apoptosis in malignant cells [1]. BCL-2 overexpression is implicated in the survival of acute myeloid leukemia (AML) cells and treatment resistance [2,3]. In a phase II trial, VEN monotherapy was investigated for the treatment of AML in the relapsed/refractory and front-line settings and produced a modest response, with an objective response rate (ORR) of 19% [4]. Subsequent studies of combination therapy of VEN with hypomethylating agents (HMAs) or low-dose cytarabine (LDAC) have demonstrated much better responses. In older, treatment-naïve AML patients, phase 1/2 studies have shown a complete remission (CR)/complete remission with incomplete hematologic recovery (CRi) rate of 62% for VEN in combination with LDAC and 67% for VEN in combination with HMAs [5,6].

In the relapsed/refractory setting, data on VEN combination therapy is currently limited to retrospective studies [7,8]. The most frequent grade 3/4 adverse events with VEN combination therapy thus far reported are cytopenias, which can be dose limiting [5,9]. Given the

Abbreviations: AML, acute myeloid leukemia; ANC, absolute neutrophil count; BCL-2, b-cell lymphoma 2; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; CTCAE, common terminology criteria for adverse events; ECOG, eastern cooperative oncology group; ELN, European LeukemiaNet; FLT3, Fms-like tyrosine kinase 3; G-CSF, granulocyte colony-stimulating factor; HMA, hypomethylating agent; IDH2, isocitrate dehydrogenase 2; LDAC, low-dose cytarabine; MRSA, methicillin-resistant Staphylococcus aureus; NPM1, nucleophosmin 1; ORR, objective response rate; OS, overall survival; PR, partial remission; PFS, progression-free survival; RBC, red blood cell; RUNX1, runt-related transcription factor 1; TP53, tumor protein 53; VEN, venetoclax

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VENETOCLAX (escalada de dosis) día v.o. + azacitidina 75 mg/m^2 días 1-7 iv/ 28 días

VENETOCLAX

\+ MICAFUNGINA

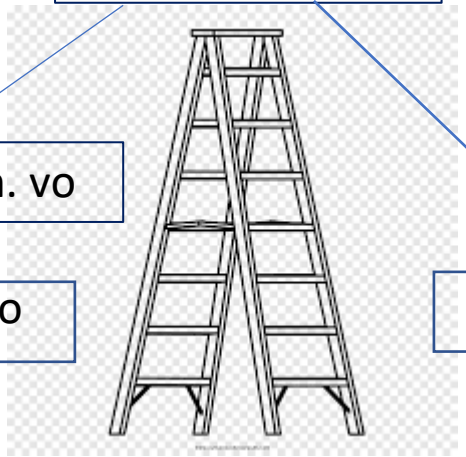
400 mg/24 h. vo

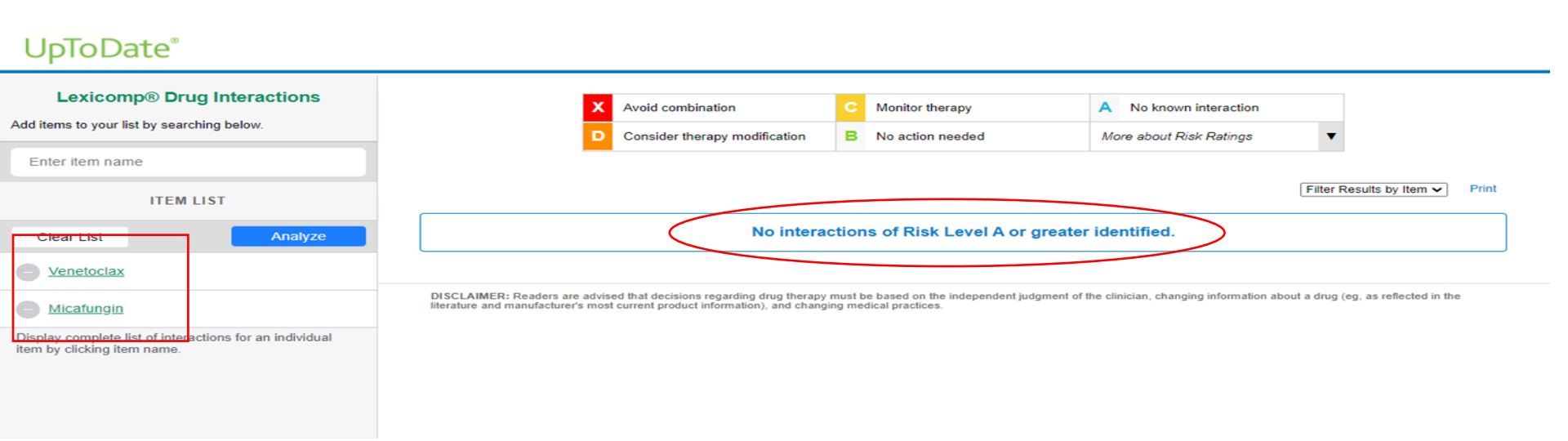
200 mg/24 h. vo

100 mg/24 h. vo

\+ POSACONAZOL

100 mg/24 h. vo





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WEBINAR V JORNADA ONCOFARMA

Actualización en el manejo de la Leucemia Mieloide Aguda en el paciente adulto y pediátrico

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How I treat acute myeloid leukemia in the era of new drugs

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The acute myeloid leukemia (AML) treatment landscape has changed substantially since 2017. New targeted drugs have emerged, including venetoclax to target B-cell lymphoma 2, midostaurin and gilteritinib to target FLT3, and ivosidenib and enasidenib to target mutant isocitrate dehydrogenase 1 and 2, respectively. Other additions include reapproval of gemtuzumab ozogamicin to target CD33, glasdegib to target the hedgehog pathway, and a liposomal formulation of daunorubicin and cytarabine (CPX-351). Genomically heterogeneous AML has a tendency to evolve, particularly under selective treatment pressure. For decades, treatment decisions have largely centered around chemotherapy drug intensity. Physicians now have access to an increasing number of drugs with novel mechanisms of action and distinctive side-effect profiles. Key issues faced by hematologists in this era of new drugs include (1) the timely identification of actionable mutations at diagnosis and at relapse; (2) deciding which drug to use among several therapeutic options; and (3) increasing awareness of how to anticipate, mitigate, and manage common complications associated with these new agents. This article will use 3 case presentations to discuss some of the new treatment challenges encountered in AML management, with the goal of providing practical guidance to aid the practicing physician. (Blood. 2020;135(2):85-96)

Introduction

Prior articles in the How I Treat series on acute myeloid leukemia (AML) have focused on acute promyelocytic leukemia, treatment of hematologic emergencies, intensive chemotherapy, management of older individuals, patients with hyperleukocytosis or preexisting comorbidities, and relapsed and refractory FLT3-mutant AML (Table 1). The recent wave of new drug approvals by the US Food and Drug Administration (FDA) (Tables 2 and 3) has created overlapping treatment options, especially in older, unfit populations, as well as in refractory/relapsed patients. Although these new therapies are a welcome advance for patients with AML, this "abundance of riches" also introduces new challenges for the treating physician. Key issues now include (1) the need for timely identification of actionable mutations, not just at diagnosis but also at relapse, (2) deciding which drug to use when several therapeutic options may be available, and (3) the need for increased awareness of how to anticipate, mitigate, and manage common complications associated with these new agents. Most clinical trial publications do not inform clinicians about how to manage emergent toxicities, and review papers predominantly focus on efficacy. In this newest addition to the How I Treat AML series, we present 3 case studies that illustrate how we select and use some of the recently approved AML therapies in the clinic, with practical guidance pertaining to the management of anticipated drug-related complications.

Patient 1: an elderly woman with previously untreated AML

A 75-year-old woman presented with progressive shortness of breath and fatigue over a 6-month period. Blood work demonstrated: a white blood count (WBC) of 26 × 10^9/L with 79% blasts; hemoglobin, 89 g/dL; neutrophils, 0.76 × 10^9/L; and platelets, 28 × 10^9/L. The bone marrow was infiltrated with 94% myeloblasts that were immunophenotypically CD34+, CD117+, CD13+, and CD33+. The karyotype showed trisomy 13, and molecular profiling revealed RUNX1, ASXL1, and SRSF2 mutations. Biochemistry revealed a mildly increased serum lactate dehydrogenase (1.3× upper limit of normal [ULN]) and creatinine (1.4× ULN). She had an Eastern Cooperative Oncology Group (ECOG) performance score of 2.

Question Should this patient receive intensive chemotherapy (ie, 7 + 3 plus or minus gemtuzumab ozogamicin [GO], CPX-351, low-dose cytarabine [LDAC] plus or minus glasdegib or venetoclax, or a hypomethylating agent [HMA] plus or minus venetoclax)?

Proposed treatment

For all patients and wherever possible, enrollment in a clinical trial is our first consideration. Additionally, we recommend rapid screening for actionable mutations (ie, FLT3, isocitrate dehydrogenase 1 and 2 [IDH1 and IDH2]), as FLT3 inhibitors, ivosidenib, or enasidenib, respectively, are either FDA approved or listed in the National Comprehensive Cancer Network (NCCN) compendium for patients ≥75 years, or considered unfit for intensive chemotherapy.

Although some older patients benefit from intensive chemotherapy, several prognostic scoring systems are available that estimate early mortality with intensive chemotherapy in patients ≥65 years with various comorbidities. Given her age of ≥75 years, her baseline renal impairment, and an ECOG ≥ 2, the risk of early mortality was likely to be high.[1] In addition, the European

Table 4. Summary of our recommendations for venetoclax administration

Issue	Management
Target drug doses	Venetoclax 400 mg/d × 28 d + azacitidine 75 mg/m² days 1-7 or decitabine 20 mg/m² daily days 1-5 subcutaneously or IV OR Venetoclax 600 mg/d × 28 d + LDAC 20 mg/m² daily days 1-10 subcutaneously
Prevention of TLS	Identify patients with higher risk of TLS: WBC >25 × 10^9/L, uric acid above 7.5 mg/dL (446 μmol/L), creatinine above 1.4 mg/dL (124 μmol/L) All patients, especially those with an elevated risk of TLS should be hospitalized until at least completion of ramp-up dosing Prior to commencing venetoclax • For patients with hyperleukocytosis, commence hydroxycarbamide or flat-dose ara-C, eg, 100-1000 mg IV daily until the WBC is <25 × 10^9/L prior to starting venetoclax • Commence TLS prophylaxis with prehydration and uricosuric agents and normalize potassium, inorganic phosphorus, and uric acid levels according to institutional practice • For some molecularly defined AML subsets with high sensitivity to venetoclax, eg, newly diagnosed NPM1 or IDH mutation, we have noticed TLS may even occur in patients with a WBC <25 × 10^9/L; such patients should be monitored carefully for rapid cytoreduction and early onset of severe hyperkalemia; in such cases, we also consider lowering the starting WBC <10 × 10^9/L to lower TLS risk prior to initiation of venetoclax Ramp-up initial venetoclax dosing in steps: 100 mg day 1, 200 mg day 2, 400 mg day 3 (for HMA), 600 mg day 4 (for LDAC) Monitor for TLS complications predose (<4 h) and 6-8h after each ramp-up dose with additional monitoring until normalization of abnormal biochemistry If significant biochemical or clinical TLS is observed, delay further venetoclax dosing until resolution
Optimize venetoclax dosing	Take venetoclax within 30 min after a meal with ~1 cup of water If HMA used, consider antiemetic prophylaxis (eg, ondansetron) Before commencing venetoclax, patients should have at least a 3-day washout from drugs with CYP3A4 inhibitor activity, as well as grapefruit juice, Seville oranges, and starfruit; CYP3A4 inducers should be avoided; the venetoclax dose ramp-up should reach 400 mg before combination with CYP3A4 inhibitors is commenced; for combination with moderate CYP3A4 inhibitors (eg, ciprofloxacin, fluconazole, or isavuconazole), reduce the venetoclax daily dose by 50% (eg, from 400 mg to 200 mg); if strong CYP3A4 inhibitors are used (eg, voriconazole or posaconazole), we recommend reducing the venetoclax daily dose by at least 75% (eg, from 400 mg to 100 mg); pharmacokinetic studies have shown that venetoclax 50 mg daily when coadministered with posaconazole 300 mg daily most closely resembles the pharmacokinetic characteristics of venetoclax 400 mg daily without posaconazole; therefore, for patients with persistent venetoclax-related adverse events (eg, neutropenia) when coadministered with strong CYP3A4 inhibitors, a further dose reduction of venetoclax to 50 mg should be considered.
Preventing infection	Severe and prolonged neutropenia is common with these regimens, even after achieving remission. For patients with grade 4 neutropenia (<0.5 × 10^9/L), antifungal prophylaxis according to institutional practice; if CYP3A4 inhibitors are used (eg, ciprofloxacin and/or azole antifungals), venetoclax dose adjustment is required (see optimizing venetoclax dosing) Hospitalization until hematologic recovery should be considered for selected patients with a high risk of complications or inadequate social support networks to enable safe outpatient management Treatment-related neutropenia may occur in the later part of the cycle and recover rapidly with commencement of G-CSF
Managing myelosuppression	Postinduction marrow assessment should be performed on days 21-28; if blast excess persists, commence the next cycle without treatment dose interruption If marrow blasts <5%, hold venetoclax and start next cycle when there has been at least partial hematologic recovery (neutrophils ≥0.5 × 10^9/L and platelets ≥50 × 10^9/L); G-CSF may be used to accelerate neutrophil recovery if neutrophils <0.5 × 10^9/L In subsequent cycles (for patients with <5% marrow blasts), monitor blood counts ~ weekly; if treatment-related grade 4 neutropenia persists for >7 days, or the patient develops severe complications, interrupt venetoclax dosing, and start G-CSF until neutrophil recovery We do not reduce the venetoclax dose to manage myelosuppression Consider shortening venetoclax duration for subsequent cycles if hematologic recovery takes >14 days after interrupting venetoclax for neutropenia and/or thrombocytopenia; the following stepwise reductions could be considered 28 days → 21 days → 14 days; consider reducing HMA dose intensity by 50% if marrow cellularity is 15% to 30%, or to 33% dose intensity if marrow cellularity <15% in the setting of clinical response with delayed or lack of hematologic recovery Prophylactic G-CSF after HMA (day 8) or LDAC (day 11) could be considered for patients with recurrent dose delays due to neutropenia
Patients with hepatic impairment	In subjects with severe hepatic impairment (Child-Pugh C), reduce venetoclax dose by 50%
Patients with renal impairment	If GFR >30 mL/min, no venetoclax dose adjustment is necessary If GFR <30 mL/min, no literature exists on venetoclax pharmacokinetics

ara-C, cytarabine; GFR, glomerular filtration rate; TLS, tumor lysis syndrome. See Table 2 for expansion of other abbreviations.

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Optimize venetoclax dosing	Take venetoclax within 30 min after a meal with ~1 cup of water If HMA used, consider antiemetic prophylaxis (eg, ondansetron) Before commencing venetoclax, patients should have at least a 3-day washout from drugs with CYP3A4 inhibitor activity, as well as grapefruit juice, Seville oranges, and starfruit[11]; CYP3A4 inducers should be avoided; the venetoclax dose ramp-up should reach 400 mg before combination with CYP3A4 inhibitors is commenced; for combination with moderate CYP3A4 inhibitors (eg, ciprofloxacin, fluconazole, or isavuconazole), reduce the venetoclax daily dose by 50% (eg, from 400 mg to 200 mg); if strong CYP3A4 inhibitors are used (eg, voriconazole or posaconazole), we recommend reducing the venetoclax daily dose by at least 75% (eg, from 400 mg to 100 mg); pharmacokinetic studies have shown that venetoclax 50 mg daily when coadministered with posaconazole 300 mg daily most closely resembles the pharmacokinetic characteristics of venetoclax 400 mg daily without posaconazole[11]; therefore, for patients with persistent venetoclax-related adverse events (eg, neutropenia) when coadministered with strong CYP3A4 inhibitors, a further dose reduction of venetoclax to 50 mg should be considered.

Management of toxicities associated with targeted therapies for acute myeloid leukemia: when to push through and when to stop

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The recent advent of myriad targeted therapies for acute myeloid leukemia (AML) has led to new hope for our patients but has also introduced new challenges in managing the disease. For clinicians, the ability to treat AML in the outpatient setting with novel agents of equal or greater efficacy than 7+3 has been transformative. Despite the enthusiasm, however, the reality is that many patients are still frail and remain at risk for treatment-related complications. Translating the results of clinical trials into improved outcomes for these individuals requires an understanding of how best to manage the adverse effects of these agents. Which patients benefit most and what to watch for? When to stop therapy? Using illustrative case presentations, this review details the unique toxicities associated with each of the approved mutation-specific and nonspecific targeted drugs for AML. The goal of this review is to help clinicians determine the risk:benefit ratio in decision making for individual patients with AML.

LEARNING OBJECTIVES
- Learn how to manage the most common toxicities of targeted therapies for AML to continue therapy and improve clinical outcomes
- Recognize unique and/or life-threatening adverse effects of targeted therapies that warrant rapid intervention and drug discontinuation

Introduction

Clinicians who treat patients with acute myeloid leukemia (AML) have for decades familiarized themselves with the risks of high-dose chemotherapy, specifically the need for prolonged hospitalization and the management of life-threatening cytopenia, sepsis, and organ failure. Over the years, innumerable prognostic models have been developed that purport to predict the "fitness" and appropriateness of individual patients to withstand 7+3 therapy.[1,2] On the basis of these models, older patients with newly diagnosed AML were often offered palliation over definitive chemotherapy.[3,4] Selecting appropriate patients capable of withstanding and benefiting from 7+3 therapy has remained complications. Translating the results of clinical trials into improved outcomes for these individuals requires an understanding of how best to manage the distinctive adverse effects of these agents to prolong and preserve quality of life.

This review article discusses the unique toxicities associated with currently approved targeted therapies for AML, including both mutation-specific and nonspecific agents. Each section uses specific patient scenarios to illustrate the decision making for individual patients and includes specific recommendations for when to proceed with therapy and when to stop.

Drug name	Dose and frequency	Toxicity	When to push through	When to stop drug
Venetoclax/HMAs (azacitidine or decitabine) or low-dose cytarabine[23,47]	400 mg orally once per day (azacitidine or decitabine) or 600 mg orally once per day (low-dose cytarabine)	Myelosuppression, tumor lysis, neutropenia, anemia, thrombocytopenia	First 2 cycles result in mild to moderate renal dysfunction, hepatotoxicity, cytopenias	Reduce dose by 50% for severe liver impairment (Child-Pugh score for cirrhosis). Hold if bone marrow evaluation on days 21 to 28 shows cytoreduction (<5% blasts). In responding patients, consider truncating duration of venetoclax therapy to 7 to 21 days in subsequent cycles; discontinue after 2 to 4 cycles if there is no response.

25/01/21

- ✓ Paciente mejora sin picos febriles con descenso en analítica de RFA y se retira oxigenoterapia.
- ✓ 10 días en tratamiento con meropenem+linezolid se suspende tto.
- ✓ Afebril, sin oxigenoterapia y estable HD.

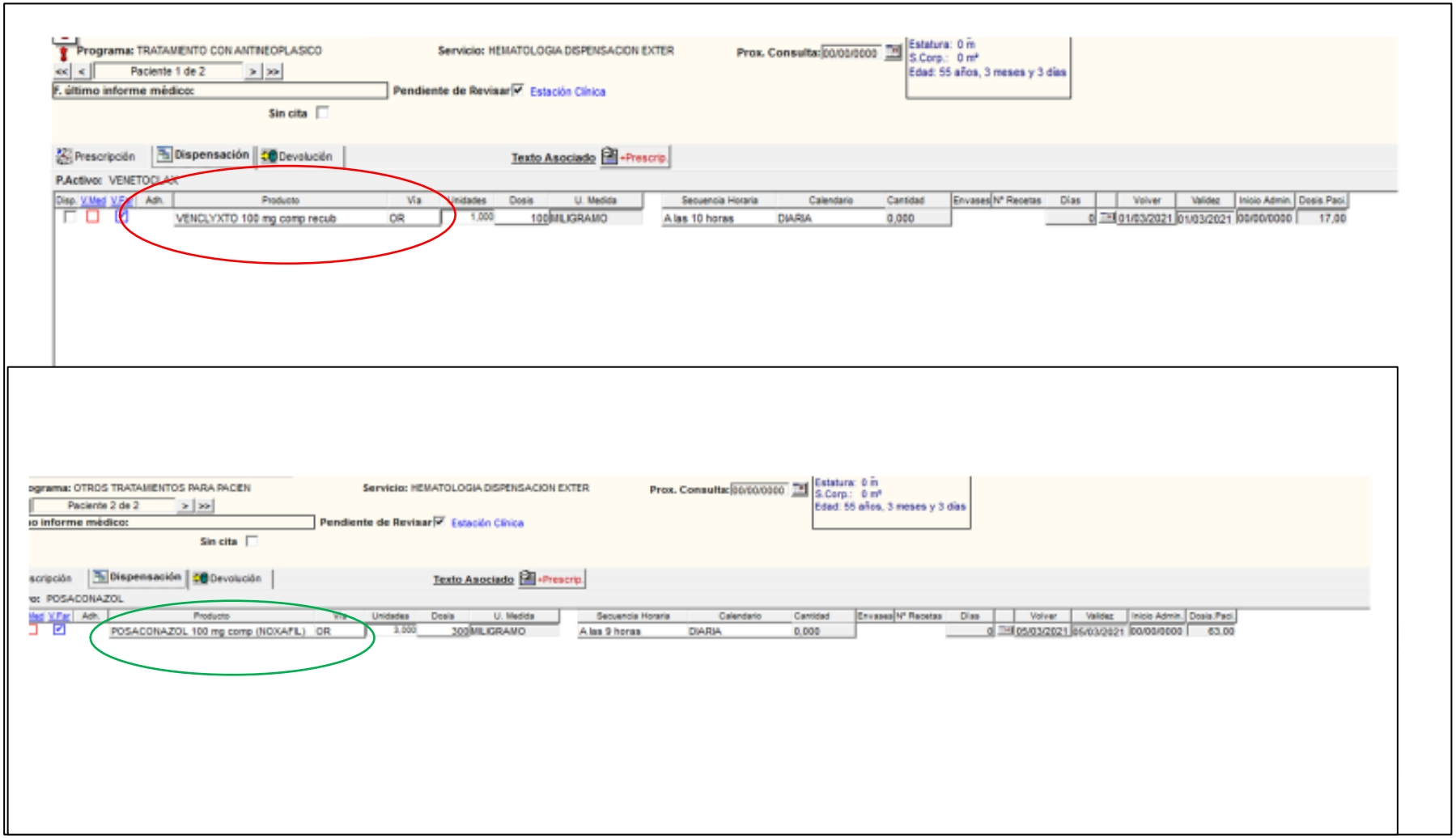
29/01/21

- ✓ Buena tolerancia esquema de azacitidina + venetoclax. Sin datos analíticos de SLT.

01/02/21

- ✓ Astenia, disnea de moderados esfuerzos.
- ✓ Transfusión de plaquetas.
- ✓ Alta médica

- ✓ Venetoclax 100mg comp.: 1 comp./24 h.
- ✓ Posaconazol 100 mg comp.: 3 comp/24 h.
- ✓ Cotrimoxazol 400/80 mg comp: 1 comp. L,X,V /12 h.
- ✓ Aciclovir 800 mg comp.: 1 comp. /12 h.
- ✓ Alopurinol 300 mg comp.: 1 comp. /12h.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Servicio: HEMATOLOGIA DISPENSACION EXTER
Prox. Consulta: 00/00/0000
Paciente 1 de 2
F. último informe médico:
Pendiente de Revisar
Estación Clínica
Sin cita
Estatura: 0 m
S.Corp.: 0 m²
Edad: 55 años, 3 meses y 3 días
Prescripción
Dispensación
Devolución
Texto Asociado
+Prescrip
P.Activo: VENETOCLAX
Producto
Vía
Unidades
Dosis
U. Medida
Secuencia Horaria
Calendario
Cantidad
Envases
Nº Recetas
Días
Volver
Validez
Inicio Admin.
Dosis Paci.
VENCLYXTO 100 mg comp recub
OR
1,000
100
MILIGRAMO
A las 10 horas
DIARIA
0,000
01/03/2021
01/03/2021
00/00/0000
17,00
Programa: OTROS TRATAMIENTOS PARA PACIEN
Servicio: HEMATOLOGIA DISPENSACION EXTER
Prox. Consulta: 00/00/0000
Paciente 2 de 2
Pendiente de Revisar
Estación Clínica
Sin cita
Estatura: 0 m
S.Corp.: 0 m²
Edad: 55 años, 3 meses y 3 días
Dispensación
Devolución
Texto Asociado
+Prescrip
POSACONAZOL
Producto
Unidades
Dosis
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Secuencia Horaria
Calendario
Cantidad
Envases
Nº Recetas
Días
Volver
Validez
Inicio Admin.
Dosis.Paci.
POSACONAZOL 100 mg comp (NOXAFIL)
OR
3,000
300
MILIGRAMO
A las 9 horas
DIARIA
0,000
05/03/2021
06/03/2021
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63,00

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VENCLYXTO® (Venetoclax)

- **¿Qué es y para qué se utiliza?**

Venclyxto® cuyo principio activo es venetoclax, es un medicamento utilizado para tratar la leucemia linfocítica crónica (LLC) en monoterapia o:

- en combinación con rituximab en pacientes adultos que hayan recibido al menos un tratamiento previo
- en combinación con obinutuzumab en pacientes adultos sin tratamiento previo.

- **¿Cómo se administra?**

La dosis de inicio es de 20 mg de venetoclax una vez al día durante 7 días. La dosis se aumenta de forma gradual durante un periodo de 5 semanas, hasta alcanzar la dosis diaria de 400 mg.

SEMANA	*DOSIS (mg)*
1	20
2	50
3	100
4	200
5	400

El comprimido debe tomarse entero por vía oral **junto con las comidas** para evitar el riesgo de pérdida de eficacia. Tómelo siempre **a la misma hora** junto con un vaso de agua. No se pueden ni triturar ni fraccionar ni masticar. Durante el tratamiento con Venclyxto® deben evitarse los productos que contengan pomelo, las naranjas amargas y la carambola (fruta estrella). Si va a iniciar un nuevo medicamento o va a tomar algún producto de herbolario consúltelo primero con su farmacéutico.

Si olvida tomar una dosis de Venclyxto® y no han trascurrido más de 8 horas, debe tomar la dosis olvidada. En caso de que hayan transcurrido más de 8 horas, no tome esa dosis y continúe con la pauta habitual al día siguiente.

- **¿Qué efectos secundarios pueden aparecer?**

Como todos los medicamentos, Venclyxto® puede tener efectos adversos, lo cual no significa que vayan a aparecer en todos los pacientes.

- Pueden aparecer muy frecuentemente: Fatiga, problemas digestivos (diarrea, náuseas, vómitos, estreñimiento), infecciones del tracto respiratorio superior, alteraciones hematológicas.
- También podrían aparecer, aunque con menor frecuencia: Sepsis, infección del tracto urinario, aumento de los niveles de ácido úrico, aumento de los niveles de creatinina en sangre.
- Acuda a urgencias si presenta superior a 38º o de más de 2 días de evolución.

- **Conservación:**

No utilice Venclyxto® después de la fecha de caducidad que aparece en el envase. La fecha de caducidad es el último día del mes que se indica.
Este medicamento no requiere condiciones especiales de conservación.

- **Contacto**

Si tiene alguna duda respecto al medicamento puede contactar con Farmacia en el teléfono: 917277072 ó 912071641 ó por mail: pacext.hulp@salud.madrid.org

Horario de atención a Pacientes Externos:
Lunes -Viernes: 8:30-14.45; y de 15:30-17.00.

- **Recuerde que:**

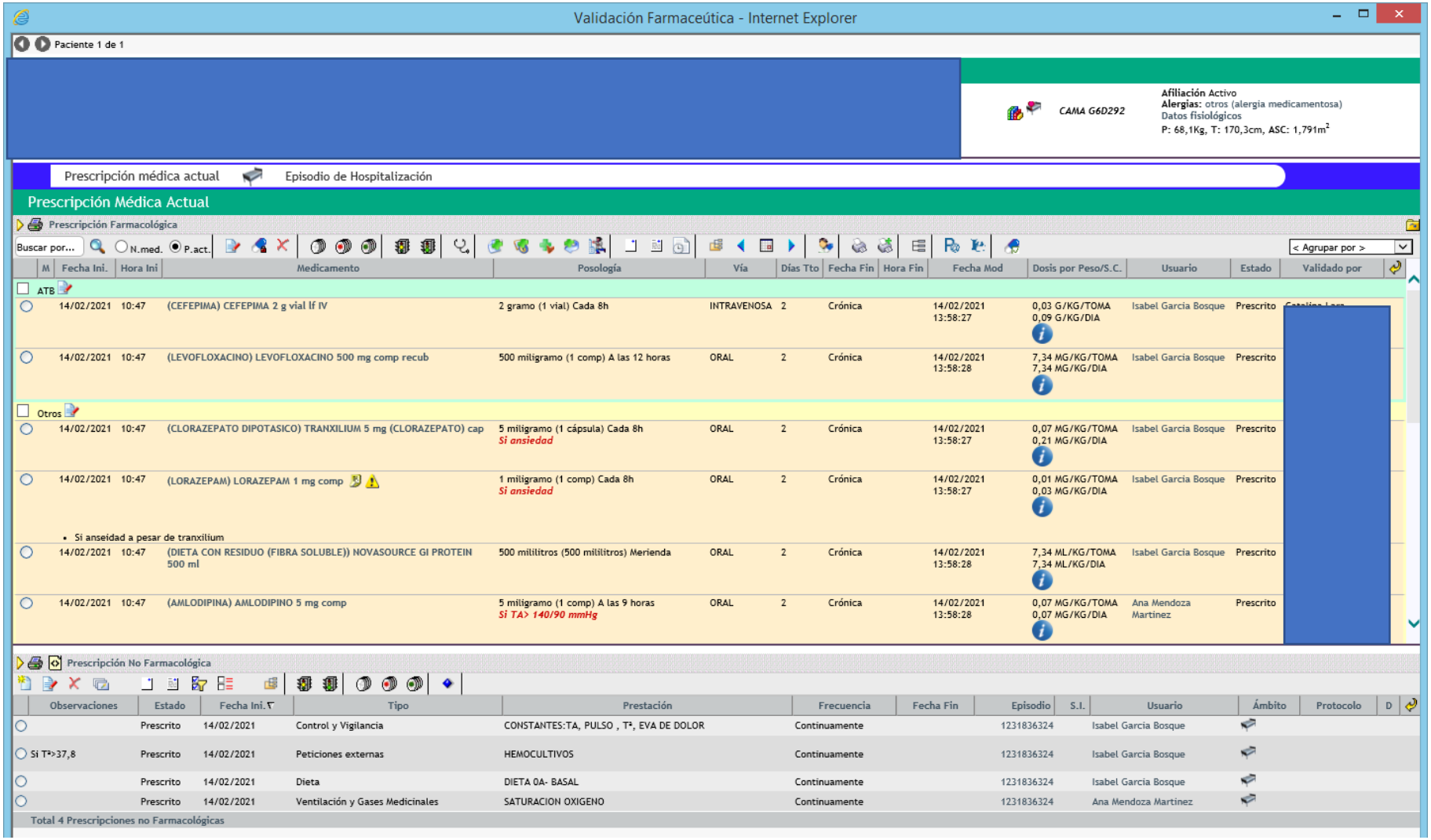
Tome su medicamento exactamente como le ha indicado su médico.
Informe a su médico o farmacéutico si está tomando o ha tomado recientemente otros medicamentos, incluso los adquiridos sin receta.
Conserve sus medicamentos, siempre que sea posible, en su envase original.
Devuelva la medicación no utilizada a la farmacia del hospital.

14/02/21

- ✓ Ingresa por fiebre.
- ✓ Cefepime y levofloxacino por antecedente foco pulmonar.
- ✓ Día + 23 (1º ciclo de azacitidina-ventoclax):
  RC con EMR -.

17/02/21

- ✓ Afebril.
- ✓ Cefepime 2g/8 h.
- ✓ Pauta para 18/02/21 el 2º ciclo de azacitidina+ venetoclax



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Actualización en el manejo de la Leucemia Mieloide Aguda en el paciente adulto y pediátrico

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¡GRACIAS!