

GRUPO ESPAÑOL DE CITOLOGÍA HEMATOLGICA

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PROPUESTA DE ESTUDIO CLÍNICO BIOLÓGICO DE PACIENTES DIAGNOSTICADOS DE LEUCEMIA MIELOIDE AGUDA QUE DEBUTAN CON CONCENTRACIONES DE PLAQUETAS EN S.P. SUPERIORES A $300 \times 10^9/L$

Isabel Rodenas, Mari-Luz Amigo, Tzu-Hua Chen-Liang MD, M. Dolores Garcia-Malo, Andrés Jerez, Francisco José Ortuño Giner
S. de Hematología y Oncología Médica. H. Morales Meseguer´
Murcia

CONTACTOS: Isabel Rodenas Quiñonero (isaa.rq3@gmail.com)

Francisco Jose Ortuño Giner (fortunog@sehh.es)

I.INTRODUCCION, REVISION Y ANALISIS DE LA CASUISTICA DE NUESTRO SERVICIO, ESBOZO DE LA PROPUESTA AL GECH Y FUNDAMENTO.

Las leucemias agudas mieloides (LMA) *de novo* son un grupo heterogéneo de neoplasias originadas en precursores mieloides con diverso grado de diferenciación. Su expresión fenotípica es muy variable, lo que responde a la gran diversidad de las alteraciones citogenéticas y moleculares que subyacen en la génesis de la enfermedad.

En su debut clínico la LMA cursa habitualmente con expansión de la clona o clonas neoplásicas e insuficiencia medular, esto es, citopenias en los elementos terminales de todas las líneas hematopoyéticas, unas por afectación directa y otras por desplazamiento, aunque el grado de afectación de las líneas no tumorales es desigual y en algunos pocos casos inexistente.

En relación a este último grupo, es de destacar la existencia de casos con LMA *de novo* no M3 que debutan con concentraciones de plaquetas normales o elevadas (LMA_{hiplt}) y/o con megacariocitos normales o incluso elevados en número en médula ósea. Esta infrecuente situación ha tenido poco reflejo en la literatura científica: las series existentes hacen referencia, a la transformaciones de síndromes mieloproliferativos crónicos (SMPC) en LMA (LMAs) o bien recogen casos de LMA *de novo* aislados. Hasta donde nosotros hemos podido indagar, no existe ningún trabajo publicado en los últimos 20 años que aborde de una manera sistemática esta particular presentación biológica, aunque es de destacar que incluso revisiones pivotaes recientes ponen de manifiesto esta situación inhabitual(,CBM4,).

Las LMA_{hiplt} se han relacionado con alteraciones citogenéticas estructurales que implican a la región 3q26 con diferentes *partners* (,C2,T15,), aunque también se han descrito en alteraciones numéricas del cromosoma 7, con i17q y en menor frecuencia con otras alteraciones cariotípicas y/o moleculares. Desde el punto de vista molecular, y partiendo de los estudios que evaluaban las mutaciones de Jak2 en el contexto de LMAs, el estudio de Jak2 en LMA *de novo* ha sido abordado en diferentes trabajos. Su incidencia (2,7%) es inferior a la encontrada en las LMAs (8,3%)(,C7,). Además su perfil biológico no parece corresponder al de las LMA_{hiplt}, aunque las series que los describen presentan resultados dispares e incluso opuestos (,C3,C4,C7,).

Para demostrar la relevancia de la cuestión, hemos revisado nuestra propia casuística de LMA_{hiplt}. En nuestra serie de 257 LMA *de novo*, se han detectado 26 casos (10%) que debutaron con concentraciones de plaquetas en s.p. superiores a $150 \times 10^9/L$, cuatro de ellos con concentraciones $>300 \times 10^9/L$ (población diana -PD-) y uno de estos casos con concentraciones $>400 \times 10^9/L$. Respecto a los cuatro casos de nuestra PD: solo uno presentó alteraciones del cromosoma tres en el contexto de un cariotipo complejo. Todos tuvieron una SG inferior a 14m (en dos casos de un mes).

Yendo un paso mas alla y con el objeto de determinar el impacto clínico y por tanto la viabilidad del trabajo, hemos evaluado el valor pronóstico de la concentración de plaquetas en el debut (además de otros factores) en un subgrupo de LMA no M3 que fueron tratadas con quimioterapia intensiva (n=77). Probablemente como consecuencia del limitado número de pacientes, el análisis mediante curvas ROC objetivo el mejor punto de discriminación en $100 \times 10^9/L$ y con este, el análisis univariante objetivó una asociación significativo con peor SG

(RR= 2,792, IC 95% 1,154-6,753, p= 0,023) en tanto que el análisis multivariante observó una tendencia (RR=2,792, IC 95% 0,896-8,698, p=0,076).

Desde nuestro punto de vista, los resultados anteriores confirman la existencia de diferencias clínicas entre los pacientes con concentraciones de plaquetas bajas y aquellos con concentraciones superiores avalando estudios ulteriores.

En base a lo expuesto anteriormente, planteamos un estudio cuyo objetivo es caracterizar el perfil de las LMA^{hipl}t no M3 que han recibido tratamiento intensivo mediante la definición de sus características clínicas, bioquímicas, hematológicas y genéticas, así como la respuesta de la enfermedad a los tratamientos en términos de SLE y SG. Para ello, la propuesta que se hace al GECH es un estudio retrospectivo de este grupo de pacientes que incluya características clínicas y biológicas y las compare con una población apareada con una concentración de plaquetas inferior a 300x10⁹/L y, potencialmente, con una segunda población que podría corresponder a LMAs.

En el contexto de los hallazgos genéticos, y eventualmente, tres objetivos secundarios podrían ser: a/ el determinar los eventos genéticos “driver” cariotípicos y/o moleculares, b/ el análisis de alteraciones moleculares específicas de línea que justifiquen el incremento de la actividad de la serie megacariocítica con particular interés en los factores de diferenciación inicial de la serie megacariocítica, factores transcripción y factores de maduración plaquetar incluyendo posibles interrupciones de la vía Jak/STAT, así como, en última instancia, c/ el hallazgo de alteraciones moleculares/proteicas susceptibles de abordaje terapéutico específico.

II.DATOS A RECOGER

Demográficos: Fecha diagnóstico, edad, sexo.

Antecedentes clínicos: diagnóstico de SMPc previo (fecha de diagnóstico, genética previa [CG y BM] y tratamientos), diagnóstico de otras neoplasias previas (hematológicas o no)(citogenética previa y tratamientos), tratamientos citostáticos por conectivopatías, exposición laboral/demográfica.

Clínica al debut: Fenómenos hemorrágicos/trombóticos. Exp. Física: diátesis, bazo/hepatomegalia.

Datos biológicos, incluyendo en este grupo los mas relevantes de bioquímica (al menos f. hepática, renal, ferritina y LDH); coagulación (TP, APTT, dímero D), hemogramas hemograma (WBC, BL%,Hb, Plq, VPM) y frotis, estudio medular (displasia, y blastos).

Médula ósea: subtipo WHO, datos AM: BL%, morfología BL, (Mk número, Mk morfología: grandes, hiperlobados(alce), bulbosos, formando *clusters*; normales; pequeños, hipolobados, monolobados, núcleos separados.

linmunofenotipo (CF o IHQ), **CG convencional (crítico)** y **FISH**, BM (toda la efectuada al diagnóstico), Jak2VAF. **y/o eventualmente la existencia de material para poder efectuar estudios ulteriores.**

Respuesta clínica y biológica: tipo de tratamiento, RC(nº Ciclos; fecha; singularidades hemograma salida (citopenias –tiempo hasta RAN >1000 Hb>10, trombocitosis).

Trasplante (TASPE/AloTMO –relacionado/haplo- y MA/RIC-.

Status actual/último; fecha de último seguimiento.

Importante: Todos los datos de este apartado se pueden “retocar” de modo que coincidan con los de vuestras bases de datos y así su obtención os lleve el mínimo tiempo posible.

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