Sociedad Chilena de Hematología

HOSPITAL CLINICO UNIVERSIDAD DE CHILE

Workshop
Leucemia Linfática Crónica 2016
Caso Clínico 2

Dr. Miguel López Cáceres
Residente Hematología
Hospital Clínico José Joaquín Aguirre

- Paciente Masculino de 70 años
- FONASA
- Profesor de Filosofía de la Universidad de Chile a cargo de 200 alumnos
- ECOG 0

Antecedentes

- Médicos: DM2NIR
- Quirúrgicos: (-)
- Alergias (-)
- Hábitos: Tabaco (+) IPA 15 OH (+) ocasional Drogas (-)
- Fármacos: Metformina 850 mg/día

Historia clínica

- Febrero 2015:
- Se recibe paciente en Hospital Clínico de la Universidad de Chile
- Historia de 3 meses de evolución de múltiples adenopatías cervicales, axilares e inguinales bilaterales. Con esplenomegalia palpable 5 cms bajo reborde costal.
- Viene diagnosticado con Leucemia Linfática Crónica desde extrasistema.

	22/08/2014	19/11/2014	08/02/2015
HTO	48	45	46
Hb	16,2	15,5	15,7
Plaquetas	226	154	170
Leucocitos	13,87	31,18	34,02
Linfocitos	7,5	22,45	26,55

	22/08/2014	19/11/2014	08/02/2015
Creat	0,9	0,9	0,8
Bili T	0,6	0,9	0,8
FA	76	69	70
GOT	23	32	33
GPT	30	40	37
GGT	33	37	34

Citometría de flujo sangre periférica Enero de 2015

- 67% de células linfoides B clonales con expresión de CD19, CD20, CD45, CD5, CD23, CD38, CD43 y CD200.
- Negativas para expresión T (CD3, CD4, CD8)
- Restricción a cadena Kappa

- **Inmunofenotipo compatible con síndrome linfoproliferativo de estirpe B con restricción a cadena Kappa, variedad Leucemia Linfática Crónica.**

- TAC: múltiples adenopatías cervicales, mediastínicas (una de 12 cms), retroperitoneales, ilíacas de hasta 8 cms e inguinales
- Biopsia ósea con infiltración 80% por linfocitos de gran tamaño, algunos con nucleolos. Las 3 poblaciones se encuentran normales.
- B2 microglobulina 5,8 mg/L

- Presenta doblaje de recuento de recuento de linfocitos en 3 meses e incluso triplica recuento.
- Además múltiples adenopatías con una mediastínica mayor a 10 cms
- Se solicita Del (17p) y mutación región variable cadena pesada, pero no se realiza por imposibilidad económica

- Se cataloga como una LLC Rai II y Binet B. Enfermedad Activa.

iwCLL à International Workshop in Chronic Lymphocytic Leukemia

- Esplenomegalia masiva
- Linfonodos de más de 10 cms
- Doblaje de recuento de linfocitos en menos de 6 meses

Estudios genéticos de relevancia actual

An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data

*The International CLL-IPI working group**

	Overall survival events	Adverse factor	Regression coefficient	Hazard ratio (95% CI)	p value	Assigned risk score
Training dataset (n=1214)	462 (38%)					
TP53 status	-	Deleted or mutated	1·434	4·2 (3·2–5·5)	<0·0001	4
IGHV mutational status	-	Unmutated	0·950	2·6 (2·1–3·2)	<0·0001	2
β_2-microglobulin concentration	-	>3·5 mg/L	0·678	2·0 (1·6–2·4)	<0·0001	2
Clinical stage	-	Rai I–IV or Binet B–C	0·464	1·6 (1·3–1·9)	<0·0001	1
Age	-	>65 years	0·555	1·7 (1·4–2·1)	<0·0001	1

- **Del(11q) à su pronóstico ha mejorado gracias al uso de FCR**
- **ZAP 70, CD38**

The international CLL-IPI working group, an international prognostic index for patients with CLL, lancet oncology 2016 17:779-90

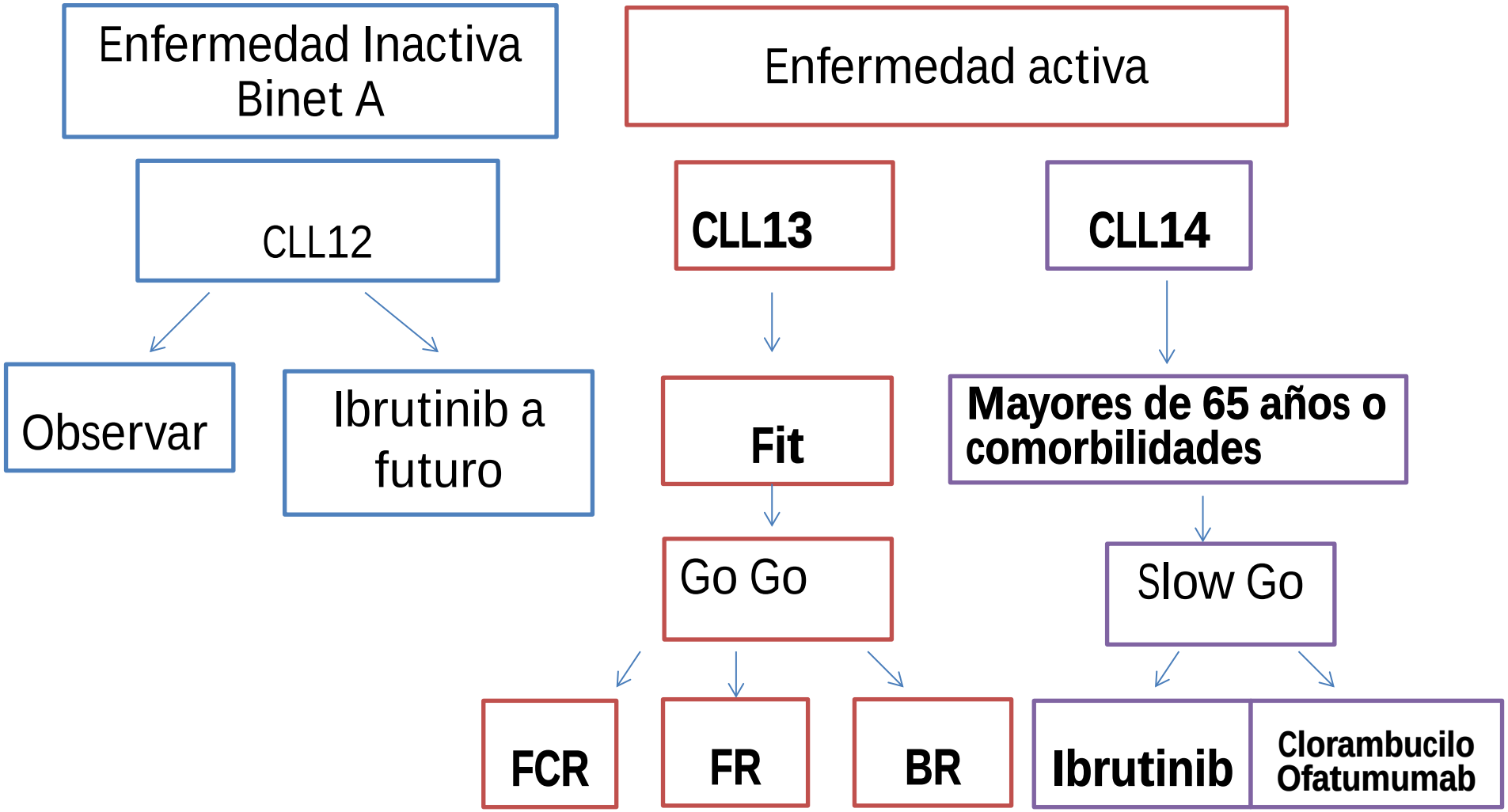
- Paciente con 4 puntos de score CLL-IPI à Riesgo intermedio – 82 % sobrevida a 5 años

- **Pacientes con del(17p) o mutación TP53 tienen un alto riesgo de refractariedad y recaída por lo que debiesen ser ingresados a estudios clínicos con uso de nuevas drogas (antagonistas de Bruton Kinasas, IPK3 y antagonistas de BCL-2) o ser candidatos a trasplante alogénico HLA compatible con quimioterapia no mieloablativa**

Clasificación de los pacientes según evaluación geriátrica

- Go à Pueden recibir el tratamiento standard
- Slow à Candidatos a recibir dosis reducida
- No à Candidatos a tratamiento paliativo

Balduci L, *Oncologist* 2000; 5:224-237


Enfermedad Inactiva
Binet A
Enfermedad activa
CLL12
CLL13
CLL14
Observar
Ibrutinib a futuro
Fit
Mayores de 65 años o comorbilidades
Go Go
Slow Go
FCR
FR
BR
Ibrutinib
Clorambucilo
Ofatumumab

Inicio FCR

- Inicia FCR a dosis disminuidas (50%)
- Rituximab + fludarabina+ ciclofosfamida
  - 1º ciclo: 03.03.15
  - 2º ciclo: 30.03.15
  - 3º ciclo: 27.04.15
  - 4º ciclo: 01.06.15

VOLUME 27 · NUMBER 4 · FEBRUARY 1 2009

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

CLINICAL TRIALS AND OBSERVATIONS

Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial

Kirsten Fischer,[1] Jasmin Bahlo,[1] Anna Maria Fink,[1] Valentin Goede,[1] Carmen Diana Herling,[1] Paula Cramer,[1] Petra Langerbeins,[1] Julia von Tresckow,[1] Anja Engelke,[1] Christian Maurer,[1] Gabor Kovacs,[1] Marco Herling,[1] Eugen Tausch,[2] Karl-Anton Kreuzer,[1] Barbara Eichhorst,[1] Sebastian Böttcher,[3] John F. Seymour,[4] Paolo Ghia,[5] Paula Marlton,[6,7] Michael Kneba,[3] Clemens-Martin Wendtner,[1,8] Hartmut Döhner,[2] Stephan Stilgenbauer,[2] and Michael Hallek[1,9]

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Key Points

- Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL.
- Updated results on safety and efficacy of the CLL8 trial.

Despite promising results with targeted drugs, chemoimmunotherapy with fludarabine, cyclophosphamide (FC), and rituximab (R) remains the standard therapy for fit patients with untreated chronic lymphocytic leukemia (CLL). Herein, we present the long-term follow-up of the randomized CLL8 trial reporting safety and efficacy of FC and FCR treatment of 817 treatment-naïve patients with CLL. The primary end point was progression-free survival (PFS). With a median follow-up of 5.9 years, median PFS were 56.8 and 32.9 months for the FCR and FC group (hazard ratio [HR], 0.59; 95% confidence interval [CI], 0.50-0.69, $P < .001$). Median overall survival (OS) was not reached for the FCR group and was 86.0 months for the FC group (HR, 0.68; 95% CI, 0.54-0.89, $P = .001$). In patients with mutated IGHV (IGHV MUT), FCR improved PFS and OS compared with FC (PFS: HR, 0.47; 95% CI, 0.33-0.68, $P < .001$; OS: HR, 0.62; 95% CI, 0.34-1.11, $P = .1$). This improvement remained applicable for all cytogenetic subgroups other than del(17p). Long-term safety analyses showed that FCR had a higher rate of prolonged neutropenia during the first year after treatment (16.6% vs 8.8%; $P = .007$). Secondary malignancies including Richter's transformation occurred in 13.1% in the FCR group and in 17.4% in the FC group ($P = .1$). First-line chemoimmunotherapy with FCR induces long-term remissions and highly relevant improvement in OS in specific genetic subgroups of fit patients with CLL, in particular those with IGHV MUT. This trial was registered at www.clinicaltrials.gov as #NCT00281918. (*Blood*. 2016;127(2):208-215)

- Persistencia clínica de adenopatías cervicales y TAC Junio muestra adenopatías mediastínicas 8 cms e ilíacas 4 cms. Linfocitosis 8000. Respuesta Parcial.

- Dada buena tolerancia a 4 primeros ciclos de decide aumentar dosis de QMT al 75%. Rituximab + Fludarabina + Ciclofosfamida
- 5º ciclo: 30.06.15
- 6º ciclo: 29.07.15
- 7º ciclo: 27.08.15
- 8º ciclo: 16.10.15

- TAC de Octubre 2015 à Persiste con adenopatía submaxilar derecha 3 cms e ilíacas de 4 cms. Sin adenopatías axilares, mediastínicas ni inguinales. Hemograma con 5000 linfocitos.

Segunda línea de tratamiento

- Progresa después de 2 años à Repetir primera línea de tratamiento
- Refractariedad o Progreso antes de 2 años
  - Fit à Go Go à Ibrutinib, venetoclax, idelalisib + R, lenalidomide + R, BR, trasplante alogénico
  - Slow Go à Ibrutinib, venetoclax, idelalisib + R, lenalidomide, ofatumumab

Comité: Rituximab + Bendamustina

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Bendamustine Combined With Rituximab in Patients With Relapsed and/or Refractory Chronic Lymphocytic Leukemia: A Multicenter Phase II Trial of the German Chronic Lymphocytic Leukemia Study Group

Kirsten Fischer, Paula Cramer, Raymonde Busch, Stephan Stilgenbauer, Jasmin Bahlo, Carmen D. Schweighofer, Sebastian Böttcher, Peter Staib, Michael Kiehl, Michael J. Eckart, Gabriele Kranz, Valentin Goede, Thomas Elter, Andreas Bühler, Dirk Winkler, Michael Kneba, Hartmut Döhner, Barbara F. Eichhorst, Michael Hallek, and Clemens-Martin Wendtner

Kirsten Fischer, Paula Cramer, Jasmin Bahlo, Carmen D. Schweighofer, Gabriele Kranz, Valentin Goede, Thomas Elter, Barbara F. Eichhorst, Michael Hallek, Clemens-Martin Wendtner, University Hospital of Cologne, Cologne; Raymonde Busch, Institute for Medical Statistics and Epidemiology of the Technical University, Munich; Stephan Stilgenbauer, Andreas Bühler, Dirk Winkler, Hartmut Döhner, University Hospital of Ulm, Ulm; Sebastian Böttcher, Michael Kneba, University Hospital of Kiel, Kiel; Peter Staib, Sankt Antonius Hospital, Eschweiler; Michael Kiehl, Department of Internal Medicine, Hospital Frankfurt/Oder, Frankfurt/Oder; Michael J. Eckart, Internistische Schwerpunkt Praxis Naegelsbacherstrasse, Erlangen, Germany.

Submitted November 17, 2010; accepted May 12, 2011; published online ahead of print at www.jco.org on August 15, 2011.

Supported by research grants from F. Hoffmann-La Roche and Mundipharma. The German Chronic Lymphocytic Leukemia Study Group receives financial support from German Cancer Aid.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this

A B S T R A C T

Purpose
The objective of this trial was to evaluate safety and efficacy of bendamustine combined with rituximab (BR) in patients with relapsed and/or refractory chronic lymphocytic leukemia (CLL).

Patients and Methods
Seventy-eight patients, including 22 patients with fludarabine-refractory disease (28.2%) and 14 patients (17.9%) with deletion of 17p, received BR chemoimmunotherapy. Bendamustine was administered at a dose of 70 mg/m^2 on days 1 and 2 combined with rituximab 375 mg/m^2 on day 0 of the first course and 500 mg/m^2 on day 1 during subsequent courses for up to six courses.

Results
On the basis of intent-to-treat analysis, the overall response rate was 59.0% (95% CI, 47.3% to 70.0%). Complete response, partial response, and nodular partial response were achieved in 9.0%, 47.4%, and 2.6% of patients, respectively. Overall response rate was 45.5% in fludarabine-refractory patients and 60.5% in fludarabine-sensitive patients. Among genetic subgroups, 92.3% of patients with del(11q), 100% with trisomy 12, 7.1% with del(17p), and 58.7% with unmutated *IGHV* status responded to treatment. After a median follow-up time of 24 months, the median event-free survival was 14.7 months. Severe infections occurred in 12.8% of patients. Grade 3 or 4 neutropenia, thrombocytopenia, and anemia were documented in 23.1%, 28.2%, and 16.6% of patients, respectively.

Conclusion
Chemoimmunotherapy with BR is effective and safe in patients with relapsed CLL and has notable activity in fludarabine-refractory disease. Major but tolerable toxicities were myelosuppression and infections. These promising results encouraged us to initiate a further phase II trial evaluating the BR regimen in patients with previously untreated CLL.

J Clin Oncol 29:3559-3566.

- 1º ciclo: 12.11.15
- 2º ciclo: 28.12.15
- Se realiza control con TAC que muestra persistencia de adenopatías ilíacas y cervical > 3 cms. Por lo que se decide continuar con esquema BR:
- 3° ciclo: 29/02/2016
- 4° ciclo: 29/03/2016
- 5° ciclo:01/05/2016
- 6° ciclo: 12/07/16
- **Control de Agosto 2016 à remisión hemograma y sin adenopatías palpables ni al TAC.**

	09/08/2016	13/09/2016	02/11/2016
HTO	30	31	35
Hb	10,4	10,4	12
Plaquetas	63000	175000	185000
Leucocitos	6900	13700	22200
Linfocitos	4300	8200	12600

Sin adenopatías al TAC de Octubre 2016

Citometría de flujo sangre periférica de Octubre 2016

- Presencia de una significativa población de linfocitos B con restricción clonal Kappa y cuyo fenotipo a pesar de la débil expresión de CD5 es sugerente de LLC, destacando la pérdida de expresión de CD20.

- Se solicita estudio genético, el cual se encuentra pendiente.

¿Opciones terapéuticas?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia

J.A. Burger, A. Tedeschi, P.M. Barr, T. Robak, C. Owen, P. Ghia, O. Bairey, P. Hillmen, N.L. Bartlett, J. Li, D. Simpson, S. Grosicki, S. Devereux, H. McCarthy, S. Coutre, H. Quach, G. Gaidano, Z. Maslyak, D.A. Stevens, A. Janssens, F. Offner, J. Mayer, M. O'Dwyer, A. Hellmann, A. Schuh, T. Siddiqi, A. Polliack, C.S. Tam, D. Suri, M. Cheng, F. Clow, L. Styles, D.F. James, and T.J. Kipps, for the RESONATE-2 Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 13, 2014 VOL. 370 NO. 11

Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia

Richard R. Furman, M.D., Jeff P. Sharman, M.D., Steven E. Coutre, M.D., Bruce D. Cheson, M.D., John M. Pagel, M.D., Ph.D., Peter Hillmen, M.B., Ch.B., Ph.D., Jacqueline C. Barrientos, M.D., Andrew D. Zelenetz, M.D., Ph.D., Thomas J. Kipps, M.D., Ph.D., Ian Flinn, M.D., Ph.D., Paolo Ghia, M.D., Ph.D., Herbert Eradat, M.D., Thomas Ervin, M.D., Nicole Lamanna, M.D., Bertrand Coiffier, M.D., Ph.D., Andrew R. Pettitt, Ph.D., F.R.C.Path., Shuo Ma, M.D., Ph.D., Stephan Stilgenbauer, M.D., Paula Cramer, M.D., Maria Aiello, M.A., Dave M. Johnson, B.S., Langdon L. Miller, M.D., Daniel Li, Ph.D., Thomas M. Jahn, M.D., Ph.D., Roger D. Dansey, M.D., Michael Hallek, M.D., and Susan M. O'Brien, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 28, 2016 VOL. 374 NO. 4

Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia

Andrew W. Roberts, M.B., B.S., Ph.D., Matthew S. Davids, M.D., John M. Pagel, M.D., Ph.D., Brad S. Kahl, M.D., Soham D. Puvvada, M.D., John F. Gerecitano, M.D., Ph.D., Thomas J. Kipps, M.D., Ph.D., Mary Ann Anderson, M.B., B.S., Jennifer R. Brown, M.D., Ph.D., Lori Gressick, B.S., Shekman Wong, Ph.D., Martin Dunbar, Dr.P.H., Ming Zhu, Ph.D., Monali B. Desai, M.D., M.P.H., Elisa Cerri, M.D., Sari Heitner Enschede, M.D., Rod A. Humerickhouse, M.D., Ph.D., William G. Wierda, M.D., Ph.D., and John F. Seymour, M.B., B.S., Ph.D.

CLINICAL TRIALS AND OBSERVATIONS

Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110δ, for relapsed/refractory chronic lymphocytic leukemia

Jennifer R. Brown,[1] John C. Byrd,[2] Steven E. Coutre,[3] Don M. Benson,[2] Ian W. Flinn,[4] Nina D. Wagner-Johnston,[5] Stephen E. Spurgeon,[6] Brad S. Kahl,[7] Celeste Bello,[8] Heather K. Webb,[9] Dave M. Johnson,[9] Sissy Peterman,[9] Daniel Li,[9] Thomas M. Jahn,[9] Brian J. Lannutti,[9] Roger G. Ulrich,[9] Albert S. Yu,[9] Langdon L. Miller,[9] and Richard R. Furman[10]

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Key Points

- Idelalisib was evaluated in 54 patients with heavily pretreated chronic lymphocytic leukemia, and target inhibition was documented in vivo.
- Oral idelalisib therapy demonstrated a favorable safety profile and rapidly induced durable disease control in the majority of patients.

In a phase 1 trial, idelalisib (GS-1101, CAL-101), a selective inhibitor of the lipid kinase PI3Kδ, was evaluated in 54 patients with relapsed/refractory chronic lymphocytic leukemia (CLL) with adverse characteristics including bulky lymphadenopathy (80%), extensive prior therapy (median 5 [range 2-14] prior regimens), treatment-refractory disease (70%), unmutated *IGHV* (91%), and del17p and/or TP53 mutations (24%). Patients were treated at 6 dose levels of oral idelalisib (range 50-350 mg once or twice daily) and remained on continuous therapy while deriving clinical benefit. Idelalisib-mediated inhibition of PI3Kδ led to abrogation of Akt phosphorylation in patient CLL cells and significantly reduced serum levels of CLL-related chemokines. The most commonly observed grade ≥3 adverse events were pneumonia (20%), neutropenic fever (11%), and diarrhea (6%). Idelalisib treatment resulted in nodal responses in 81% of patients. The overall response rate was 72%, with 39% of patients meeting the criteria for partial response per IWCLL 2008 and 33% meeting the recently updated criteria of PR with treatment-induced lymphocytosis.[1,2] The median progression-free survival for all patients was 15.8 months. This study demonstrates the clinical utility of inhibiting the PI3Kδ pathway with idelalisib. Our findings support the further development of idelalisib in patients with CLL. These trials were registered at clinicaltrials.gov as #NCT00710528 and #NCT01090414. (*Blood*. 2014;123(22):3390-3397)

CLINICAL TRIALS AND OBSERVATIONS

Outcomes of CLL patients treated with sequential kinase inhibitor therapy: a real world experience

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Key Points

- Toxicity was the most common reason for discontinuation of ibrutinib or idelalisib in treated patients with CLL.
- KI-intolerant patients, but less so those with CLL progression, can be successfully treated with an alternate KI.

B-cell receptor kinase inhibitor (KI) therapy represents a paradigm shift in chronic lymphocytic leukemia (CLL) management, but data on practice patterns after KI discontinuation and optimal sequencing are limited. We conducted a multicenter, retrospective, comprehensive analysis on 178 patients with CLL (ibrutinib = 143; idelalisib = 35) who discontinued KI therapy. We examined responses, toxicity, post-KI therapies, and overall survival (OS). Patients had a median of 3 prior therapies (range 0-11); del17p (34%), p53 mutation (27%), del11q (33%), and complex karyotype (29%). Overall response rate (ORR) to first KI was 62% (complete response 14%). The most common reasons for KI discontinuation were toxicity (51%), CLL progression (29%), and Richter transformation (RT) (8%). Median progression-free survival (PFS) and OS from KI initiation were 10.5 and 29 months, respectively. Notably, initial KI choice did not impact PFS or OS; however, RT portended significantly inferior OS (P = .0007). One hundred fourteen patients received subsequent salvage therapy following KI discontinuation with an ORR to subsequent KI at 50% and a median PFS of 11.9 months. Median PFS in KI-intolerant patients treated with an alternate KI was not reached vs 7 months for patients with CLL progression. In summary, these data demonstrate that toxicity was the most common reason for KI discontinuation, that patients who discontinue KI due to toxicity can respond to an alternate KI, and that these responses may be durable. This trial was registered at www.clinicaltrials.gov as #NCT02717611 and #NCT02742090. (*Blood.* 2016;128(18):2199-2205)

Del(17p) TP53

Venetoclax in relapsed o leukaemia with 17p dele phase 2 study

Stephan Stilgenbauer, Barbara Eichhorst, Johannes Schete
Clemens-Martin Wendtner, Andrew W Roberts, Wojciech J
Monali Desai, Brenda Chyla, Maria Verduga, Sari Heitner E

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See Comment page 690

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Summary

Background Deletion of chromosome 17p (del[prognosis when treated with standard chemo- that induces chronic lymphocytic leukaemia c patients with relapsed or refractory chronic ly assess the activity and safety of venetoclax n lymphocytic leukaemia.

Methods In this phase 2, single-arm, multicer relapsed or refractory chronic lymphocytic l Chronic Lymphocytic Leukemia guidelines) fro Patients started once daily venetoclax with a we Patients were then given daily 400 mg contin reason. The primary endpoint was the pro independent review committee. Activity and s study drug (per protocol). This study is reg ongoing, and patients are still receiving treatm

Findings Between May 27, 2013, and June 27, 2 12·1 months (IQR 10·1–14·2), an overall res 70·5–86·6) of 107 patients. The most comm (21 [20%]), anaemia (19 [18%]), and thrombocyt irrespective of their relationship to treatment, w haemolytic anaemia (seven [7%] each), pneum the study within 30 days of the last dose of ve event (none assessed as treatment related).

Interpretation Results of this trial show that relapsed or refractory del(17p) chronic lymphc prognosis population. Additionally, in view sequencing with other novel targeted agents s lymphocytic leukaemia.

Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with *TP53* aberrations: a phase 2, single-arm trial

Mohammed Z H Farooqui, Janet Valdez, Sabrina Martyr, Georg Aue, Nakhle Saba, Carsten U Niemann, Sarah E M Herman, Xin Tian, Gerald Marti, Susan Soto, Thomas E Hughes, Jade Jones, Andrew Lipsky, Stefania Pittaluga, Maryalice Stetler-Stevenson, Constance Yuan, Yuh Shan Lee, Lone B Pedersen, Christian H Geisler, Katherine R Calvo, Diane C Arthur, Irina Maric, Richard Childs, Neal S Young, Adrian Wiestner

Summary

Background Patients with chronic lymphocytic leukaemia (CLL) with *TP53* aberrations respond poorly to first-line chemoimmunotherapy, resulting in early relapse and short survival. We investigated the safety and activity of ibrutinib in previously untreated and relapsed or refractory CLL with *TP53* aberrations.

Methods In this investigator-initiated, single-arm phase 2 study, we enrolled eligible adult patients with active CLL with *TP53* aberrations at the National Institutes of Health Clinical Center (Bethesda, MD, USA). Patients received 28-day cycles of ibrutinib 420 mg orally once daily until disease progression or the occurrence of limiting toxicities. The primary endpoint was overall response to treatment at 24 weeks in all evaluable patients. This study is registered with ClinicalTrials.gov, number NCT01500733, and is fully enrolled.

Findings Between Dec 22, 2011, and Jan 2, 2014, we enrolled 51 patients; 47 had CLL with deletion 17p13.1 and four carried a *TP53* mutation in the absence of deletion 17p13.1. All patients had active disease requiring therapy. 35 enrolled patients had previously untreated CLL and 16 had relapsed or refractory disease. Median follow-up was 24 months (IQR 12·9–27·0). 33 previously untreated patients and 15 patients with relapsed or refractory CLL were evaluable for response at 24 weeks. 32 (97%; 95% CI 86–100) of 33 previously untreated patients achieved an objective response, including partial response in 18 patients (55%) and partial response with lymphocytosis in 14 (42%). One patient had progressive disease at 0·4 months. 12 (80%; 95% CI 52–96) of the 15 patients with relapsed or refractory CLL had an objective response: six (40%) achieved a partial response and six (40%) a partial response with lymphocytosis; the remaining three (20%) patients had stable disease. Grade 3 or worse treatment-related adverse events were neutropenia in 12 (24%) patients (grade 4 in one [2%] patient), anaemia in seven (14%) patients, and thrombocytopenia in five (10%) patients (grade 4 in one [2%] patient). Grade 3 pneumonia occurred in three (6%) patients, and grade 3 rash in one (2%) patient.

Interpretation The activity and safety profile of single-agent ibrutinib in CLL with *TP53* aberrations is encouraging and supports its consideration as a novel treatment option for patients with this high-risk disease in both first-line and second-line settings.

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