# CONFERENCIAS

# ALL - Burkitt and antibody based therapies (Leucemia Linfoblástica Aguda – Burkitt: rol de la inmunoterapia)
# Acute Lymphoblastic Leukemia - Adult. Novel strategies (Leucemia Linfoblástica Aguda: nuevas estrategias terapéuticas)

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**Current diagnostic procedures** in adult acute lymphoblastic leukaemia (ALL) have the following aims: 1. confirmation of the diagnosis of ALL and determination of Band T-lineage subtypes by immunophenotyping of leukemic blast cells (LBL), 2. identification of surface antigens or fusion proteins for evaluation of Minimal Residual Disease (MRD) 3. identification of new markers, which may be either of prognostic relevance or may form the basis of new targeted therapies.

**New therapeutical approaches** include: 1. more ALL directed (e.g. Asparaginase) induction and consolidation therapies, 2. molecular targeting, 3. antibody therapy, 4. new approaches for Stem Cell Transplantation, 5. specific protocols for ALL subgroups, e.g. Adolescents or Elderly.

**Chemotherapy:** Induction therapy with the "standard" drugs steroids, Vincristin, Antracyclines, Asparaginase +/- others can achieve Complete Remission (CR) rates in adults of 80-90%. Consolidation regimen differs widely, but inclusion of High Doses of Methotrexat (HD-MTX) or Cytosin Arabinosid (HD-AraC) may – together with intrathecal prophylaxis- lead to survival rates of 35 - 50% and low CNS relapse rates (<3%). New chemotherapeutic agents explored in ALL are Nelarabine, specific for TALL and T-lymphoblastic lymphoma (T-LBL), and Clofarabine in relapsed/refractory ALL.

**Asparaginase**, the only ALL specific drug is a substantial part in the improved survival of childhood ALL and Adolescents and Young Adults (AYA), leading to survival rates of 60-70 %. Pegylated Asparaginase (PEG-Asp), with a longer Asp depletion is now explored in all age groups of ALL with promising results.

**Minimal residual disease** (MRD) is the detection of minimal residual leukaemic cells, not detectable by light microscopy. Methods for MRD are: 1. individual IGH and TCR rearrangements with PCR, 2. surface marker pattern by flow cytometry or 3. Fusion proteins by RT-PCR such as bcr-abl. International consensus for detection of MRD is by 1 LBC in 10.000 cells. MRD negativity is defined as <10-4, MRD positivity as >10-4.

MRD can be used to evaluate remission quality; molecular CR or molecular failure and for remission control. MRD levels during the course of ALL are now used for treatment decisions such as patients' selection for stem cell transplantation (SCT) in CR1.

**Molecular targeting** is relevant particularly for Ph/bcr-abl-positive ALL. With the development of abl-tyrosine kinase inhibitors such as Imatinib, Dasatinib or Nilotinib given parallel to induction therapy the CR rate increased from 75% to >90%. Monotherapy with Imatinib or Dasatinib resulted also in CR rates of more than >90%. The current question is whether all such patients should receive a SCT in CR1 or not if the remain MRD negative.

**Antibody therapy**; the use of Rituximab has substantially improved the outcome of patients with

mature B-ALL and Burkitt / Burkitt-like NHL. Rituximab is now explored in B-lineage CD20+ ALL in elderly, in CD20+ standard risk patients and as an "in vivo purging" for adult high risk B lineage CD20+ ALL before SCT. A new promising therapy is with a bispecific CD3 and CD19 directed antibody (Blinatumomab). It is effective in MRD-positive ALL patients with a molecular CR rate of 80% but also in relapsed/refractory ALL with a response rate of 60%. For adult T-ALL and T-LBL only the antibody antiCD52 (Campath) is available.

**Stem cell transplantation**; the extension is currently due to the availability of a large number (worldwide ~14 Mio.) of unrelated donors. Thus transplants are now more widely used and the survival in adult ALL seems equal to sibling allogeneic transplant. The transplants have also been extended to elderly patients (>50yrs) by the use of reduced intensity condition (RIC) regimen. Autologous transplantation may have a new revival in ALL, when MRD-negative patients are transplanted with a MRD-negative stem cell graft.

**For Adolescents** paediatric ALL strategies have obtained survival rates of 60% – 70%, which is mainly due to higher doses of asparaginase, corticosteriodes, and better time/dose adherence. Also for Elderly ALL patients with new treatment protocols for Ph+ vs. Ph- ALL patients, outcome has substantially improved.

**Conclusion:** ALL subtype oriented therapy tailored by MRD, the use of antibody therapy, molecular targeting, age adopted chemotherapy, and SCT may increase the cure rate of adult ALL patients to 50%.

# Acute Promyelocytic Leukemia as a Model for the Development of Clinical Networks in Developing Countries. The International Consortium on Acute Promyelocytic Leukemia Experience

# (Leucemia Promielocítica Aguda (LPA) como Modelo para Implementación de Redes Clínicas en Países en Desarrollo. Experiencia del Consorcio Internacional de LPA)

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Abstract: All-trans retinoic acid (ATRA) in combination with anthracyclines constitutes the backbone of contemporary therapeutic strategies for the treatment of patients with newly diagnosed acute promyelocytic leukemia (APL). The introduction of ATRA in the 1980s changed APL from a highly fatal to a highly curable illness, with contemporary clinical trials that achieved complete remission (CR) and long term disease free survival (DFS) rates of approximately 90% and 85%, respectively. The major cause of treatment failure with current therapy is death during induction mostly as a result of hemorrhage and differentiation syndrome. APL-associated coagulopathy is a particularly relevant target for medical educational programs, because it may be rapidly reversible with early administration of ATRA and by rapid initiation of supportive measures. Unfortunately, the treatment outcome of patients with APL in developing countries is still significantly inferior compared to that reported in Europe and USA, with approximately 30% of patients dying within two weeks of diagnosis, mainly due to hemorrhage, and with mortality rates during consolidation of about 10%. This is in contrast to developed countries, where the rate of early deaths ranges between 3.7-7.3% and deaths during consolidation occur in only 1.3-11% in of patients. Consequently, in developing countries, the long term overall survival (OS) is below 60% in adults and children whereas it exceeds 85% in developed countries. The International Consortium on Acute Promyelocytic Leukemia (IC-APL) was established in 2005 as an initiative of the International Members Committee of the American Society of Hematology with the aim of creating a network of institutions in Brazil, Mexico, Uruguay and Chile that would exchange experiences and data with centers in the US and Europe. IC-APL formulated treatment guidelines based on the PETHEMA2005 protocol, except that idarubicin was replaced by daunorubicin. A key feature of the protocol was the use of the anti-PML immunofluorescence test as a tool for rapid diagnosis of APL allowing immediate initiation of ATRA treatment and blood product support. In addition, regular web-based meetings were organized, in which case by case discussions were held in order to direct the best standard of care. This also provided a focus for careful documentation of specific outcomes and ongoing monitoring of treatment efficacy and toxicity. One hundred eighty three eligible patients were enrolled from June 2006 through September 2010. One hundred fifty three (85%) patients achieved complete hematological remission, 27 patients (15%) died during induction and 3 were lost to follow up. After a median follow up of 28 months, the 2-year cumulative incidence of relapse (CIR), overall survival (OS) and disease-free survival (DFS) were 4.5%, 80% and 91%, respectively.

# Hacia una hematología integrativa

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La Oncología Integrativa es una concepción en pleno crecimiento en Estados Unidos y Oriente, pero en desarrollo en Europa y Latinoamérica.

Está dirigida a cubrir la demanda de los pacientes y la insatisfacción de los profesionales en un mundo en crisis económica y de los sistemas de salud.

Muchos consideran a la Medicina Integrativa como un sinónimo de alternativa, pero no es así.

Medicinas alternativas son todas aquellas terapias no contempladas por las escuelas médicas convencionales o alopáticas, incluyendo ideas y conceptos de avanzadas con prácticas cuestionables por charlatanería, y en muchos casos peligrosas y sin rigor científico.

Medicina Integrativa y Oncología Integrativa en sentido estricto incluyen ideas y prácticas más allá de la Medicina Convencional, pero sin rechazar tratamientos alopáticos de probada validez y todos los tratamientos alternativos deben estar probados científicamente.

Enfatiza en 4 principios básicos:

1) La capacidad del organismo de lograr su equilibrio (asumiendo una capacidad innata para curar, reparar, regenerar y adaptarse a la injuria o a una pérdida).
2) Enfoque integral de la persona (enfoca al paciente más allá de lo físico. entendiendo un complejo sistema de relaciones entre lo mental, emocional y lo espiritual. Estas dimensiones son fundamentales y relevantes para la salud y para llegar a un adecuado diagnóstico y tratamiento).
3) Importancia de un estilo de vida: Salud y enfermedad son el resultado de una directa relación entre genes y el estilo de vida (incluyendo dieta, actividad física, descanso y sueño, stress, calidad de relaciones y trabajo). Opciones de estilo de vida pueden influir tanto o más que los genes y deben ser volcados en la historia cínica médica.
   Medicina del estilo de vida uno de los componentes de la medicina integrativa debe darnos información y consejos a los médicos sobre cómo potenciar y tratar más efectivamente las enfermedades.
4) El rol crítico de la relación Médico-Paciente a través de la Historia: La relación Médico-Paciente fue especial casi un ritual o sacro. Cuando un médico entrenado escucha a un paciente y presta atención a su historia ya comenzó el proceso de curación, antes de que se inicie cualquier tratamiento. La gran tragedia de la medicina contemporánea es que los sistemas corporativos desempeñan este aspecto central de la práctica.

Los oncólogos integrativos deberán tener un rol principal en:

a) Ayudar a los pacientes en decisiones difíciles sobre opciones de tratamientos convencionales.
b) Ayudar a integrar al tratamiento convencional con estrategias dietarias terapias mente-cuerpo y seleccionados tratamientos alternativos de demostrada eficacia en el manejo del síntoma o de los efectos colaterales de las terapias.

c) Alertar a los pacientes sobre los riesgos y beneficios demostrados y probados de los tratamientos alternativos.
d) Educar a aquellos en riesgos de padecer cáncer sobre el estilo de vida para reducirlo.
e) Ayudar a los pacientes con cáncer incurable al mejor tratamiento paliativo.
f) Ayudar a los pacientes terminales y sus familias sobre la muerte y el proceso de morir.

La propuesta es centrar la atención en el paciente y otorgarle un rol fundamental en la toma de decisiones. Esto va a permitir al médico una mayor libertad y un alivio en compartir decisiones difíciles.

Otro aspecto prioritario es un enfoque diferente en la determinación de los riesgos y las estrategias de prevención.

El avance en medicina genómica y la secuenciación del genoma completo abre un espectro amplio de oportunidades de prevención.

Están en pleno desarrollo los consorcios de patologías oncológicas para identificar los genes más comunes y prevalentes en cada patología. Mieloma, mielodisplasia y leucemias agudas son uno de los campos con más avances. También se han confirmado las hipótesis de las células troncales tumorales con una progresión a tumor mediante la adquisición secuencial y progresiva de mutaciones.

La medicina personalizada se está convirtiendo hoy en una realidad donde se habla de patologías con una determinada mutación más que en una enfermedad única. Los costos de una secuenciación completa están cerca de 1000 USD y los secuenciadores serán cada vez más accesibles y portables.

En este punto la posibilidad de poder medir diferentes riesgos de padecer enfermedades, los patrones de metilación sobre genes ya demostrados como causales de desarrollo o progresión del tumor. Y las intervenciones del estilo de vida, manejo del stress, deporte, nutrigenómica o el uso de tratamientos preventivos con algunos complementos naturales o suplementos que tienen un rol principal.

Como corolario la Oncología Integrativa propone una medicina superadora, con un rol primordial de la medicina convencional, la única demostrada como curativa y una perfecta sinergia de prácticas complementarias de probada validez científica. Donde la única medicina personalizada viable es la enfocada en el paciente como una totalidad.

# AML 2012: Diagnosis and Classification (Leucemia Mieloblástica Aguda: diagnóstico y clasificación en el 2012)

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The diagnosis and classification of acute myeloid leukemia (AML) are based on the morphology and histopathology of bone marrow aspirate and biopsy specimens, in combination with immunophenotypic analysis and cytogenetics. More recently, the importance of molecular genetics and epigenetics has also been recognized in AML. Recurrent mutations in AML have been systematically characterized using whole-genome sequencing and several, such as FLT3, NPM1 and CEBPα, have already emerged in clinical practice as both prognostic indicators and potential drug targets. The clinical relevance of a variety of epigenetic biomarkers is under investigation. Novel clinicopathologic subgroups are being identified on the basis of both cytogenetic and molecular genetic abnormalities and clinical trials to target these specific subgroups are both underway and in development. The objective of this presentation is to review current classification systems in AML from the USA and Europe and to highlight significant changes during the last several years, with emphasis on those that have had an impact on clinical decision-making.

# An integrated genomic approach to the assessment and treatment of acute leukemia"
# (El enfoque genómico integrado a la evaluación y el tratamiento de las leucemias agudas)

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Acute leukemias are characterized by acquired somatic mutations and epigenetic alterations in genes that are crucial for hematopoietic differentiation and cellular proliferation and for survival pathways. The heterogeneity and genetic complexity of these disorders is daunting, but our expanding knowledge of the pathogenetic mechanisms underlying malignant transformation, coupled with the increasing availability of novel agents that target these pathways, offers unique opportunities for improved therapy. Currently, a patient's acute leukemia is characterized by morphologic evaluation, flow cytometry, cytogenetic analysis, and molecular studies focused on a few key genes. An integrated approach would make use of whole genome sequencing, gene expression profiling (GEP), assessment of DNA methylation patterns, microRNA expression, and single-nucleotide polymorphism (SNP) arrays. High-throughput methods capable of full genome evaluation offer a revolutionary change in the way we diagnose, characterize, and treat both AML and ALL. Full sequencing of a cancer genome or transcriptome will be affordable for routine clinical care within the decade. Sequencing the first 2 cytogenetically normal AML genomes unexpectedly revealed 10-15 somatic mutations, a number remarkably similar to that seen in solid tumors. The identification of genes commonly mutated in leukemia will reveal novel pathways that can be targeted therapeutically to improve patient survival.

Microarray-based testing will define gene and miRNA expression, DNA methylation patterns, chromosomal imbalances, predisposition to disease, and chemosensitivity. The future will focus on molecular profiling of leukemia cells as well as host factors that influence the development and outcome of these diseases. GEP is accurately able to predict some of the major cytogenetic subgroups of AML, but a second application could be to predict the chemosensitivity of a patient's leukemia cells and to guide the choice of optimal chemotherapy. DNA methylation patterns can also distinguish cell types. miRNA profiling has shown that expression of these small, non-coding RNAs varies widely among cells, and this variability can be used for cell classification. While miRNA expression patterns also distinguish some of the major subclasses of AML, the true power of genome-wide miRNA profiling techniques lies in their ability to reveal insights into cellular biology not already appreciated by current methods.

The identification of chromosomal rearrangements by karyotype analysis is a powerful prognostic indicator and currently drives post-remission treatment recommendations. Genome-based techniques seek to define chromosomal changes that are less than 5 Mb in size, beyond the level of detection by traditional methods. SNP arrays are microarray-based platforms that allow the detection of single nucleotide variations at up to 900,000 separate genomic loci, at an average intermarker distance of less than 700bp. This approach allows the analysis

of DNA copy number variations (CNVs) that are not detectable by standard karyotype analysis, such as amplifications and deletions, while also yielding information about smaller regions of DNA loss, including both loss of heterozygosity (LOH) and the presence of copy-neutral LOH (sometimes referred to as uniparental disomy). However, because of their exquisite sensitivity, it is crucial that the technique be performed on leukemia (tumor) as well as matched normal DNA in order to distinguish cancer-specific lesions from constitutional changes. Thus, genomic approaches and sophisticated informatics platforms will be useful not just for clinical assessment of individuals, but also to define new cellular and molecular pathways that lead to leukemogenesis, identify new therapeutic targets, and discover new biomarkers that can be used to monitor treatment response.