UNIVERSIDADE FEDERAL DO PARÁ

INSTITUTO DE CIÊNCIAS BIOLÓGICAS

PROGRAMA DE PÓS-GRADUAÇÃO GENÉTICA E BIOLOGIA MOLECULAR

DOUTORADO EM GENÉTICA E BIOLOGIA MOLECULAR

DEJAIR DA SILVA DUARTE

LEUCEMIAS AGUDAS: uma abordagem citogenética, hematológica e bioquímica em pacientes adultos da região norte do Brasil.

BELÉM-PA

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Orientador: Dr. Rommel Mario Rodriguez Burbano.

Tese apresentada ao Programa de Pós-graduação em Genética e Biologia Molecular, Instituto de Ciências Biológicas da Universidade Federal do Pará como requisito para a obtenção do título de Doutorado em Genética e Biologia Molecular.

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Dados Internacionais de Catalogação na Publicação (CIP) de acordo com ISBD
Sistema de Bibliotecas da Universidade Federal do Pará
Gerada automaticamente pelo módulo Ficat, mediante os dados fornecidos pelo(a) autor(a)

D111l da Silva Duarte, Dejair.
Leucemias agudas: uma abordagem citogenética, hematológica e bioquímica em pacientes adultos da região norte do Brasil. / Dejair da Silva Duarte. — 2025.
132 f. : il. color.

Orientador(a): Prof. Dr. Rommel Rodriguez Burbano
Tese (Doutorado) - Universidade Federal do Pará, Instituto de Ciências Biológicas, Programa de Pós-Graduação em Genética e Biologia Molecular, Belém, 2025.

1. LEUCEMIA AGUDA. 2. CITOGENÉTICA. 3. LMA. 4. LLA. I. Título.

CDD 572.8

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Aprovado em 22 de Janeiro de 2025.

Conceito: Aprovado.

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Dedico este trabalho a minha família, à minha esposa Aliceane Aguiar e filha Selena Marie e a todos que me ajudaram nesta façanha.

AGRADECIMENTOS

Agradeço aos meus pais Jair e Dinora por todo incentivo ao meu estudo desde o ensino fundamental à pós-graduação, mesmo com poucos recursos nunca deixaram que eu ficasse sem o necessário para estudar. E principalmente a minha esposa Aliceane Aguiar por toda ajuda e compreensão nos momentos de ausência, e por cuidar tão bem da nossa riqueza e da filha Selena Marie. A minha sogra Alda Aguiar, por cuidar da minha filha quando temos que ir trabalhar e por todo cuidado conosco. As minhas cunhadas em especial a Cintya Aguiar e Ruan pelos meus afilhados e pelo notebook. E as minhas tias Duely e Arlene por serem pessoas tão especiais em nossas vidas.

Gostaria de agradecer a CAPES pela bolsa de a mim concedida para o desenvolvimento do projeto. E o meu orientador, o professor Dr. Rommel Burbano, pela confiança e orientação no projeto, permitindo abrir as portas do Hospital Ophir Loyola para o desenvolvimento do projeto, assim como todos os membros do Laboratório de Biologia Molecular. E meu coorientador professor Dr. André Khayat por orientação no projeto e na vida, e que me permite fazer parte de seu grupo de estudo no NPO, e assim ter contato com pessoas que contribuem de forma significativa para minha formação acadêmica. Entre eles meus amigos Eliel Barbosa e Marcelo Oliveira. E a todos que contribuíram de forma direta e indireta para essa façanha desde Salinas a minha casa na ilha de Outeiro. Meu muito obrigado.

“Fazer o que “tem que fazer”, a fim de fazer

o que se “pode fazer” para o que “quero fazer”.

Frase do filme O Grande Desafio

RESUMO

A leucemia aguda (LA) é um tipo de câncer no sangue que se origina na medula óssea. Sendo a alteração citogenética e a instabilidade cromossômica (IC) uma característica marcante do câncer, refletindo a taxa acelerada de aquisição de alterações cromossômicas com relevância prognóstica e terapêutica. Este estudo descreve, pela primeira vez, as alterações cariotípicas em adultos com leucemia linfoblástica aguda (LLA) e leucemia mieloide aguda (LMA) na região Norte do Brasil, correlacionando-as com características clínicas, hematológicas e bioquímicas. Por meio de bandeamento cromossômico, imunofenotipagem e análise de dados hematológicos e bioquímicos, observou-se que a aneusomia do cromossomo 21 foi a mais frequente em pacientes com LLA. As alterações estruturais mais comuns incluíram t(9;22), t(4;11), t(1;19), del(6q) e del(9p). Pacientes com t(4;11) apresentaram níveis elevados de hemácias, enquanto del(9p) foi associada a parâmetros hematológicos distintos. Alterações bioquímicas, como elevação de ureia, foram observadas em pacientes com t(4;11) e del(6q), sugerindo relação com disfunção renal e prognóstico. Em pacientes com LMA, foram identificadas translocações frequentes, como t(9;22), t(6;9), t(8;21) e t(9;11), com 14 pacientes apresentando cariótipo normal. A translocação t(9;22) mostrou correlação com alterações nos níveis de neutrófilos, eosinófilos, basófilos e bastonetes, além de variações nos níveis de glicose e potássio. O estudo destaca a relevância da instabilidade cromossômica em pacientes com LA no Norte do Brasil, com altas frequências de trissomia 21 e 8 em LLA, e associações citogenéticas significativas. Deleções como del(6q) e del(9p) foram relacionadas a desfechos desfavoráveis em LLA. Em LMA, 36% dos pacientes apresentaram instabilidade numérica, e 16% exibiram translocações, reforçando o impacto prognóstico da trissomia 8 e da monossomia 7. Sendo assim, este é um dos primeiros trabalhos a descrever que alterações citogenéticas, cariótipo normal e instabilidade cromossômica em pacientes adultos com leucemias agudas no Norte do Brasil e como tais alterações e cariótipos desempenham um papel crucial no tratamento e prognóstico. Assim como, associar alterações hematológicas e bioquímicas com alterações citogenéticas, cariótipo normal e sexo. Enfatizamos a necessidade de estudos adicionais para validar nossos achados e identificar mais marcadores genéticos associados a desfechos hematológicos e bioquímicos.

Palavras-chaves: LLA, LMA, CITOGENÉTICA, LEUCEMIA AGUDA.

ABSTRACT

Acute leukemia (AL) is a type of blood cancer that originates in the bone marrow. Cytogenetic alterations and chromosomal instability (CI) are hallmark features of cancer, reflecting the accelerated rate of acquisition of chromosomal changes with prognostic and therapeutic relevance. This study describes, for the first time, the karyotypic alterations in adults with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) in the Northern region of Brazil, correlating them with clinical, hematological, and biochemical characteristics. Through chromosomal banding, immunophenotyping, and analysis of hematological and biochemical data, it was observed that aneusomy of chromosome 21 was the most frequent in ALL patients. The most common structural alterations included t(9;22), t(4;11), t(1;19), del(6q), and del(9p). Patients with t(4;11) showed elevated red blood cell levels, while del(9p) was associated with distinct hematological parameters. Biochemical alterations, such as elevated urea levels, were observed in patients with t(4;11) and del(6q), suggesting a relationship with renal dysfunction and prognosis. In AML patients, frequent translocations were identified, including t(9;22), t(6;9), t(8;21), and t(9;11), with 14 patients displaying a normal karyotype. The t(9;22) translocation correlated with changes in neutrophil, eosinophil, basophil, and band cell levels, as well as variations in glucose and potassium levels. The study highlights the relevance of chromosomal instability in AL patients in Northern Brazil, with high frequencies of trisomy 21 and 8 in ALL and significant cytogenetic associations. Deletions such as del(6q) and del(9p) were linked to unfavorable outcomes in ALL. In AML, 36% of patients exhibited numerical instability, and 16% displayed translocations, underscoring the prognostic impact of trisomy 8 and monosomy 7. Thus, this is one of the first studies to describe cytogenetic alterations, normal karyotypes, and chromosomal instability in adult patients with acute leukemias in Northern Brazil, and how these alterations and karyotypes play a crucial role in treatment and prognosis. Additionally, it associates hematological and biochemical alterations with cytogenetic changes, normal karyotypes, and sex. We emphasize the need for further studies to validate our findings and identify additional genetic markers associated with hematological and biochemical outcomes.

Keywords: ALL (Acute Lymphoblastic Leukemia), AML (Acute Myeloid Leukemia), Cytogenetics e Acute Leukemia.

LISTA DE ABREVIATURAS E SIGLAS

DNA	Ácido desoxirribonucleico
INCA	Instituto Nacional do Câncer
LLA	Leucemia Linfoblástica Aguda
LMA	Leucemia Mieloide Aguda
LLA-B	Leucemia Linfoide de células B
SNC	Sistema Nervoso Central
LD	Livre de Doença
SG	Sobrevida Global
DRM	Doença Residual Mínima
NCCN	National Comprehensive Cancer Network
SWOG	*Southwest Oncology Group*
ISCN	International Systen for Human Cytogenomic Nomenclature
DP	Desvio Padrão

SUMÁRIO

I. REFERENCIAL TEÓRICO

I.1 LEUCEMIA

O sangue é um tecido fluido composto por leucócitos (glóbulos brancos ou WBCs), eritrócitos (glóbulos vermelhos ou RBCs) e trombócitos (plaquetas). Nas últimas décadas, observa-se um aumento significativo na incidência de doenças onco-hematológicas, entre as quais a leucemia se destaca como um dos tipos mais prevalentes e potencialmente letais. A leucemia caracteriza-se pela proliferação descontrolada de leucócitos imaturos, que se originam nos tecidos esponjosos da medula óssea, comprometendo a produção normal das células sanguíneas e, consequentemente, o funcionamento do sistema hematopoiético (Saleem *et al.*, 2022).

Dentre os subtipos de leucemia, destacam-se a leucemia mieloide aguda (LMA) e a leucemia mieloide crônica (LMC), que afetam a linhagem mieloide, bem como a leucemia linfoblástica aguda (LLA) e a leucemia linfocítica crônica (LLC), que envolvem a linhagem linfoide. Além dessas, existem variantes menos frequentes, como as leucemias de células B e T maduras e as relacionadas a células naturais killer (NK), que se originam de glóbulos brancos já diferenciados. Com o avanço das técnicas de sequenciamento de última geração (Next-Generation Sequencing - NGS) e a descoberta de novos biomarcadores, a classificação da Organização Mundial da Saúde (OMS) foi revisada em 2016, introduzindo mudanças significativas na categorização das leucemias agudas e das neoplasias mieloides em relação aos critérios tradicionais (Arber *et al.,* 2016). No mundo, em 2020, foram estimados 475 mil casos de leucemia, o que equivale a 2,5% de todos os tipos de câncer (Ferlay *et al*., 2020).

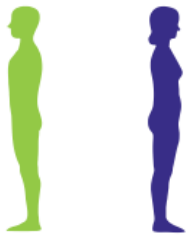
A gênese das leucemias está atribuída a fatores genéticos e ambientais, sendo os fatores de risco ambientais sendo relacionada por uma proporção pequena do número de casos da doença. Com exceção da LLA, quanto mais se avança a idade, maior a probabilidade de se desenvolver leucemia. Outros fatores de risco com evidência suficiente são tabagismo (LMA e LMC) e tratamento prévio com radioterapia ou alguns quimioterápicos (LMA e LLA). O histórico familiar (LMA e LLC), algumas síndromes genéticas (Down, anemia de Fanconi, Li-Fraumeni) e outras doenças hereditárias (LMA), infecções por HTLV-1 ou EBV (LLA) também são fatores de risco que aumentam a probabilidade de desenvolver tal doença. Entre os agentes ocupacionais cancerígenos com evidência suficiente de aumento de risco às leucemias, destaca-se a exposição ao benzeno, o formaldeído e às radiações X e gama (LMA, LMC e LLA) (American Cancer Society, c2022a; International Agency For Research On Cancer, 2019).

I.2 ESTATÍSTICA SOBRE A LEUCEMIA NO BRASIL

No Brasil, o número estimado de casos novos de leucemia para o Brasil, para cada ano do triênio de 2023 a 2025, é de 11.540 casos, o que corresponde a um risco estimado de 5,33 por 100 mil habitantes, sendo 6.250 em homens e 5.290 em mulheres. Esses valores correspondem a um risco estimado de 5,90 casos novos a cada 100 mil homens e 4,78 a cada 100 mil mulheres (INCA 2022).

Distribuição proporcional dos dez tipos de câncer mais incidentes estimados para 2023 por sexo, exceto pele não melanoma*

Localização Primária	Casos	%
Próstata	2.760	26,5%
Estômago	1.200	11,5%
Traqueia, brônquio e pulmão	880	8,5%
Cólon e reto	690	6,6%
Cavidade oral	440	4,2%
Leucemias	440	4,2%
Fígado	430	4,1%
Sistema nervoso central	320	3,1%
Esôfago	270	2,6%
Laringe	260	2,5%



Localização Primária	Casos	%
Mama feminina	2.410	22,4%
Colo do útero	1.980	18,4%
Cólon e reto	740	6,9%
Traqueia, brônquio e pulmão	650	6,0%
Estômago	630	5,9%
Leucemias	350	3,3%
Ovário	340	3,2%
Fígado	320	3,0%
Glândula tireoide	320	3,0%
Sistema nervoso central	270	2,5%

*Números arredondados para múltiplos de 10.

Figura 1. Distribuição proporcional dos dez tipos de câncer mais incidentes estimados para 2023 por sexo, exceto pele não melanoma, no Brasil.
Fonte: INSTITUTO NACIONAL DE CÂNCER JOSÉ ALENCAR GOMES DA SILVA. Estimativa da incidência e mortalidade por câncer no Brasil em 2022. Rio de Janeiro, 2022.

I.3 ESTATÍSTICA DA LEUCEMIA NA REGIÃO NORTE

A leucemia ocupa a décima posição entre os tipos de câncer mais frequentes, é o sexto câncer mais frequente nas Regiões Norte (4,53 por 100 mil), em homens. No Nordeste (5,54 por 100 mil), seguido pela Região Sudeste (5,83 por 100 mil), com a 11ª posição, sem considerar os tumores de pele não melanoma,. (INCA, 2023). Em relação aos dados epidemiológicos no Estado do Pará, com base nos dados de estimativa do INCA (2022), vemos que a incidência de casos de leucemias é maior no estado quanto para homens e mulheres em comparação com a capital.

Localização Primária	Casos	%			Localização Primária	Casos	%
Próstata	2.760	26,5%	Homens	Mulheres	Mama feminina	2.410	22,4%
Estômago	1.200	11,5%			Colo do útero	1.980	18,4%
Traqueia, brônquio e pulmão	880	8,5%			Cólon e reto	740	6,9%
Cólon e reto	690	6,6%			Traqueia, brônquio e pulmão	650	6,0%
Cavidade oral	440	4,2%			Estômago	630	5,9%
Leucemias	440	4,2%			Leucemias	350	3,3%
Fígado	430	4,1%			Ovário	340	3,2%
Sistema nervoso central	320	3,1%			Fígado	320	3,0%
Esôfago	270	2,6%			Glândula tireoide	320	3,0%
Laringe	260	2,5%			Sistema nervoso central	270	2,5%

Figura 2. Distribuição proporcional dos dez tipos de câncer mais incidentes estimados para 2023 por sexo, exceto pele não melanoma, no Brasil, na região Norte.
Fonte: INSTITUTO NACIONAL DE CÂNCER JOSÉ ALENCAR GOMES DA SILVA. Estimativa da incidência e mortalidade por câncer no Brasil 2022. Rio de Janeiro, 2022.

I.4 LEUCEMIAS AGUDAS

As leucemias agudas, que incluem a leucemia mieloide aguda (LMA) e a leucemia linfoblástica aguda (LLA), constituem um grupo diversificado de distúrbios malignos. Esses distúrbios são caracterizados por mecanismos alterados de auto renovação, proliferação e diferenciação em células progenitoras hematopoiéticas comprometidas com a linhagem mieloide ou linfoide (Rose-Inman e Kuehl, 2014; Haferlach *et al*., 2007).

As células leucêmicas, frequentemente conhecidas como blastos, apresentam várias anormalidades moleculares e/ou genéticas. Historicamente, a classificação da leucemia aguda era baseada na morfologia dos blastos e nas colorações citoquímicas. Atualmente, a classificação da Organização Mundial da Saúde (OMS) é fundamentada na linhagem, demonstrada pela expressão dos antígenos na superfície celular. Subtipos distintos dentro de cada linhagem são definidos com base na morfologia, imunofenotipagem e genética molecular (Vardiman *et al*., 2002; Duffield *et al*., 2023).

Entre as alterações citológicas observadas nestes tipos de leucemias, a citopenia ocorre quando blastos leucêmicos substituem a hematopoiese normal na medula óssea. Em outros casos, a expansão clonal faz com que blastos leucêmicos se acumulem rapidamente no sangue, resultando em leucocitose e se espalhem para os linfonodos, baço, fígado, testículos e sistema nervoso central (SNC). As manifestações clínicas podem incluir sintomas constitucionais, como febre, suores noturnos, perda de peso, hematomas fáceis, sangramento e dispneia. A doença do SNC ocorre em 5–10% dos pacientes com LLA versus 2% dos pacientes com LMA (Sancho *et al*., 2006).

Um novo paradigma emergente é que muitas anormalidades genéticas afetam vias de transdução de sinal ou vias transcricionais semelhantes, fornecendo insights sobre a fisiopatologia das leucemias agudas. Isso possibilita o uso de terapias direcionadas, que

representam uma mudança significativa em relação ao uso único de quimioterapia convencional, atualmente o principal tratamento para leucemias agudas (Chung *et al*., 2017). Além disso, a leucemogênese exige o acúmulo de alterações genômicas anormais na hematopoiese (Chung *et al*., 2017).

I.5 LEUCEMIA LINFOBLASTICA AGUDA (LLA)

A leucemia linfoide aguda (LLA) é ocasionada por uma transformação maligna oriunda da proliferação de células progenitoras linfóides da medula óssea, sangue a sítios extramedulares (Terwilliger e Abdul-Hay, 2017). A incidência de LLA segue uma distribuição bimodal, tendo um primeiro pico ocorrendo na infância e um segundo pico ocorrendo na idade de 50 anos (Paul *et al.*, 2016). Os casos de LLA ocorrem com maior frequência em crianças do que em adultos. Pacientes adultos apresentam incidência de 1 em cada 100 mil habitantes, sendo maior em adultos idosos, com diminuição da sobrevida relacionada ao avanço da idade (Noone *et al*., 2017).

Atualmente as estratégias de intensificação de dose têm levado a uma melhora significativa nos desfechos de pacientes pediátricos, entretanto o prognóstico para os idosos continua ruim. Apesar de uma alta taxa de resposta à quimioterapia de indução, estima-se que 30% a 40% dos pacientes adultos com LLA alcançarão remissão em longo prazo (Jabbour *et al.*, 2015).

A LLA foi a classificada pela primeira vez pela classificação Francesa Americana Britânica (FAB) que dividiram a LLA em 3 subtipos (L1, L2 e L3) com base no tamanho celular, citoplasma, nucléolo, vacuolação e basofilia (Bennett *et al*., 1976). A Organização Mundial de Saúde, em 1997, propôs uma classificação tendo como característica a morfologia celular e perfil citogenético dos blastos leucêmicos, e identificaram três tipos de LLA: Linfoblástico B, Linfoblástico T e Leucemia de células Burkitt.

A Leucemia de células de Burkitt foi excluída, em uma revisão em 2008, porque não é mais visto como uma entidade separada o linfoma de Burkitt e a leucemia linfoblástica B foram divididos em dois subtipos: LLA-B com anomalias genéticas recorrentes e B-LLA não especificado. Subtipos como LLA -B com anormalidades genéticas recorrentes é delineado com base no rearranjo cromossômico específico, a descrição está presente na Tabela 1 (Vardiman *et al*., 2009).

Tabela 1. Classificação das Leucemias linfoblásticas agudas segundo a OMS.
Fonte: adaptado do artigo de T Terwilliger and M Abdul-Hay (2017). ALL: a comprehensive review and 2017 update.

Leucemia linfoblástico de células B
Linfoma com hipodiploidia
Linfoma com hiperdiploidia
Linfoma com t(9; 22) (q34; q11.2) [BCR-ABL1]
Linfoma com t(v; 11q23) [rearranjo MLL]
Linfoma com t(12; 21) (p13; q22) [ETV6-RUNX1]
Linfoma com t(1; 19) (q23; p13.3) [TCF3-PBX1]
Linfoma com t(5; 14) (q31; q32) [IL3-IGH]
Linfoma com amplificação intracromossómica do cromossoma 21 (iAMP21)
Linfoma com translocações envolvendo tirosina-quinases ou receptores de citocinas (‘LLA de BCR-ABL1’)
Leucemia Linfoide de Células T
Leucemia linfoides precursora de células T precoces

Duas novas classificações provisórias foram adicionadas à lista de anormalidades genéticas recorrentes, no caso o hipodiploidia foi redefinido como hipodiploidia ou hipodiploidia com mutações de TP53 (Arber et al., 2016). Nos adultos, a LLA das células B é responsável aproximadamente por 75% dos casos, enquanto a LLA das células T compreende os restantes casos (Terwilliger, *et al.* 2017).

Recentemente a classificação consenso internacional (CCI) é uma atualização de subtipos previamente descritos na classificação da OMS de 2016, incorporando várias entidades recentemente descritas em leucemia linfoblástica aguda de células B e T conforme a tabela1. Esta classificação ICC incorpora dados clínicos, citogenéticos e moleculares recentes no caso de leucemias, que podem ajudar na apresentação de características clínicas, assim como na estratificação de risco e na seleção do tratamento para esses pacientes (Duffield *et al.*, 2023).

A Classificação de Consenso Internacional de LLA
Leucemia linfoblástica aguda B (LLA-B)
LLA-B com anomalias genéticas recorrentes
LLA-B com t(9;22)(q34.1;q11.2)/ *BCR::ABL1*
com envolvimento apenas linfoide
com envolvimento multilinhagem
LLA-B com t(v;11q23.3)/ *KMT2A* reorganizado
LLA-B com t(12;21)(p13.2;q22.1)/ *ETV6::RUNX1*
LLA-B, hiperdiplóide
LLA-B, baixo hipodiplóide
LLA-B, quase haplóide
LLA-B com t(5;14)(q31.1;q32.3)/ *IL3::* IGH
LLA-B com t(1;19)(q23.3;p13.3)/ *TCF3::PBX1*
LLA-B, *BCR::ABL1* -like, classe ABL-1 reorganizada
LLA-B, *BCR::ABL1* -like, JAK-STAT ativado
LLA-B, *BCR::ABL1* -like, NOS
LLA-B com iAMP21
LLA-B com rearranjo *MYC*
LLA-B com rearranjo *DUX4*
LLA-B com rearranjo *MEF2D*
LLA-B com rearranjo *ZNF384*
LLA-B com rearranjo *NUTM1*
LLA-B com rearranjo *HLF*
LLA-B com *UBTF::ATXN7L3/PAN3,CDX2* (“CDX2/UBTF”)
LLA-B com IKZF1 N159Y
LLA-B com PAX5 P80R
Entidades provisórias
LLA-B, *ETV6::RUNX1* -like
LLA-B, com alteração *PAX5*
LLA-B, com *ZEB2* mutado (p.H1038R)/IGH:: *CEBPE*
LLA-B, *ZNF384* reorganizado
LLA-B, *KMT2A* reorganizado
Leucemia linfoblástica aguda T (LLA-T)
Precursor precoce de células LLA-T, ativado *por BCL11B*
Precursor precoce de células LLA-T, NOS
LLA-T, NOS
Entidades provisórias
Entidade provisória: célula natural killer (NK) LLA

Tabela 2. Classificação de Consenso Internacional de LLA.
Fonte: tabela adaptadas do artigo International Consensus Classification of acute lymphoblastic leukemia/lymphoma de Duffield et al. 2023.

Assim como estudos genômicos de LLA identificaram múltiplas novas entidades com mutações condutoras distintas e perfis de expressão gênica comumente distintos, evidentes usando algoritmos de agrupamento (figura 1). Estas descobertas levaram à expansão ou revisões da classificação anterior da OMS de 2016 e a proposição de entidades provisórias para LLA tipo B e T (Duffield *et al.* 2023).

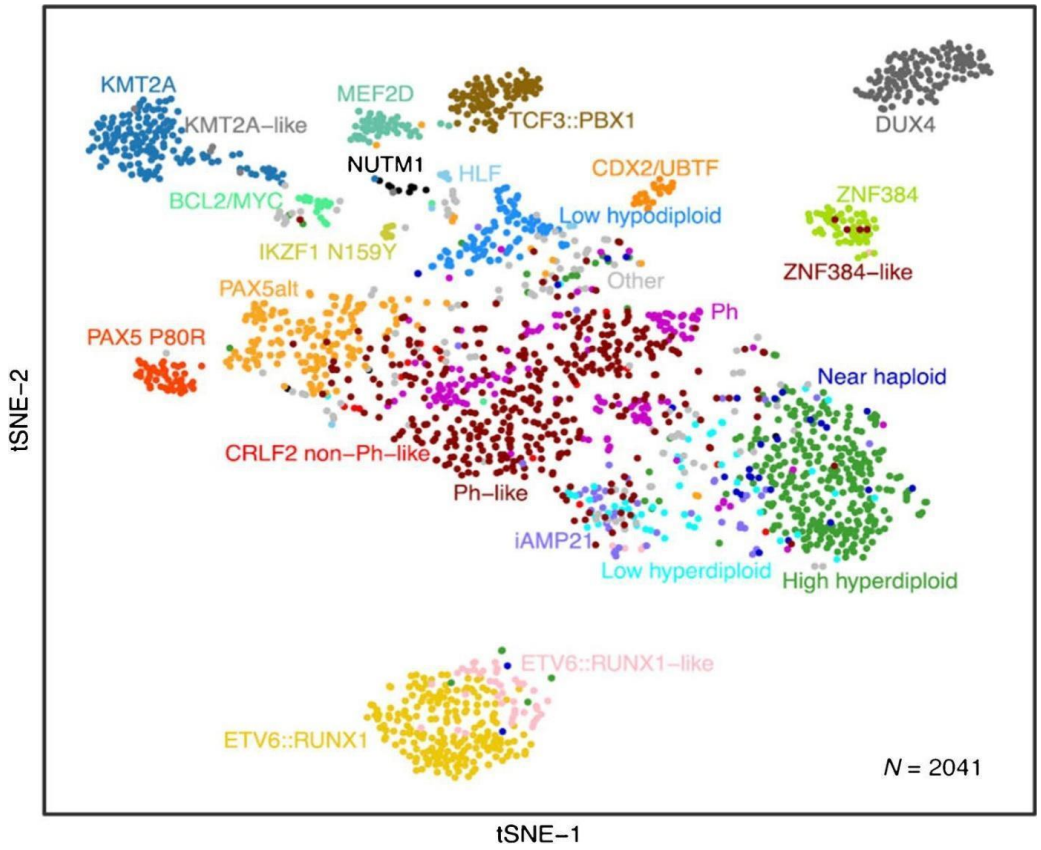


Figura 3. A figura representa o agrupamento bidimensional usando a incorporação estocástica vizinha distribuída em t de dados de sequenciamento do transcriptoma completo de 2.041 amostras de leucemia coletadas no momento do diagnóstico de crianças ou adultos com LLA (Duffield *et al*., 2023; Gu *et al.,* 2023).

I.6 LEUCEMIA MIELÓIDE AGUDA (LMA)

A Leucemia mieloide aguda (LMA) é uma condição diversa que se origina da multiplicação descontrolada de células hematopoiéticas clonais (Papaemmanuil *et al*., 2016). Esta é a leucemia aguda mais frequentemente diagnosticada em adultos, com uma idade média de diagnóstico de 68 anos (Juliusson *et al*.,2009). O diagnóstico se baseia no limiar de 20% de blastos ainda é o critério para definir LMA, atualmente, diversas alterações genéticas adicionais são consideradas como características definidoras de LMA para neoplasias mieloides com 10% ou mais de blastos na medula óssea ou no sangue (Estey *et al*.,2022). Novas descobertas moleculares relacionadas à evolução, avanço e mecanismos de resistência

da LMA tiveram um grande impacto na forma como diagnosticamos, classificaram e acompanharam pacientes com LMA (Arber *et al*., 2022). No caso, as diversas categorias pré-existentes de doenças associadas à LMA, tais como sarcoma mieloide, neoplasias mieloides ligadas à síndrome de Down e neoplasia de células dendríticas plasmocitoides blásticas, continuam as mesmas (Arber *et al*., 2022).

I.7 CLASSIFICAÇÃO DAS LEUCEMIAS AGUDAS

A LMA é caracterizada por um conjunto diversificado de doenças que são distintas em termos genéticos. A classificação revisada preserva muitas das formas de LMA anteriormente estabelecidas com alterações genéticas recorrentes e incorpora outras entidades que têm relações genéticas (Arber *et al*., 2022) (figura 3).

Classificação da LMA com porcentagem de blastos necessários para o diagnóstico
Leucemia promielocítica aguda (LPA) com t(15;17)(q24.1;q21.2)/ LMP :: RARA ≥ 10%
APL com outros rearranjos RARA * ≥ 10%
LMA com t(8;21)(q22;q22.1)/ RUNX1 :: RUNX1T1 ≥ 10%
LMA com inv(16)(p13.1q22) ou t(16;16)(p13.1;q22)/ CBFB :: MYH11 ≥ 10%
LMA com t(9;11)(p21.3;q23.3)/ MLLT3 :: KMT2A ≥ 10%
LMA com outros rearranjos KMT2A † ≥ 10%
LMA com t(6;9)(p22.3;q34.1)/ DEK :: NUP214 ≥ 10%
LMA com inv(3)(q21.3q26.2) ou t(3;3)(q21.3;q26.2)/ GATA2 ; MECOM (EVI1) ≥ 10%
LMA com outros rearranjos do MECOM ‡ ≥ 10%
LMA com outras translocações recorrentes raras (ver Tabela 5 suplementar) ≥ 10%
LMA com t(9;22)(q34.1;q11.2)/ BCR :: ABL1 § ≥ 20%
LMA com NPM1 mutado ≥ 10%
LMA com mutações CEBPA bZIP no quadro ≥ 10%
LMA e SMD/LMA com TP53 mutado † 10-19% (SMD/LMA) e ≥ 20% (LMA)
LMA e SMD/LMA com mutações genéticas relacionadas à mielodisplasia 10-19% (SMD/LMA) e ≥ 20% (LMA) Definido por mutações em ASXL1 , BCOR , EZH2, RUNX1 , SF3B1, SRSF2 , STAG2 , U2AF1 ou ZRSR2
LMA com anormalidades citogenéticas relacionadas à mielodisplasia 10-19% (SMD/LMA) e ≥ 20% (LMA) Definido pela detecção de um cariótipo complexo (≥ 3 anormalidades cromossômicas clonais não relacionadas na ausência de outras anormalidades genéticas recorrentes definidoras de classe), anormalidades clonais del(5q)/t(5q)/add(5q), −7/del(7q), +8, del(12p)/t(12p)/add(12p), i(17q), −17/add(17p) ou del(17p), del(20q) e/ou idic(X)(q13)
LMA não especificada de outra forma (NOS) 10-19% (MDS/LMA) e ≥ 20% (LMA)
Sarcoma mieloide

Tabela 3. Classificação da LMA com porcentagem de blastos necessários para diagnóstico
Fonte:Arber *et al*., 2022.

Pesquisados com experiência nos aspectos clínicos, patológicos e genéticos destas doenças desenvolveu a Classificação de Consenso Internacional (ICC) para leucemias mieloides agudas. Uma das principais mudanças inclui a eliminação do grupo de LMA com alterações relacionadas à mielodisplasia, ao mesmo tempo em que cria novas categorias de LMA com anormalidades citogenéticas relacionadas à mielodisplasia, LMA com mutações genéticas relacionadas à mielodisplasia e LMA com *TP5* mutado.

A maioria das anomalias genéticas recorrentes, incluindo mutações no NPM1, que definem subtipos específicos de LMA, tem uma necessidade menor de ≥ 10% de blastos na medula óssea ou no sangue, e uma nova categoria de SMD/LMA é criada para outros tipos de casos com 10– 19% de células blásticas observadas. Além de terapia prévia, neoplasias mieloides antecedentes ou distúrbios genéticos germinativos subjacentes que predispõem ao desenvolvimento de LMA são agora recomendados como qualificadores para o diagnóstico inicial de LMA.

Com essas mudanças, a classificação da LMA é atualizada para incluir a evolução dos achados genéticos, clínicos e morfológicos. Com base nestes dados genômicos, o ICC criou esta nova categoria e eliminou o LMA-MRC definido apenas pela displasia morfológica e fundiu a categoria anterior de LMA com *RUNX1* mutado neste grupo (Weinberg *et al.*, 2023) (figura 3).

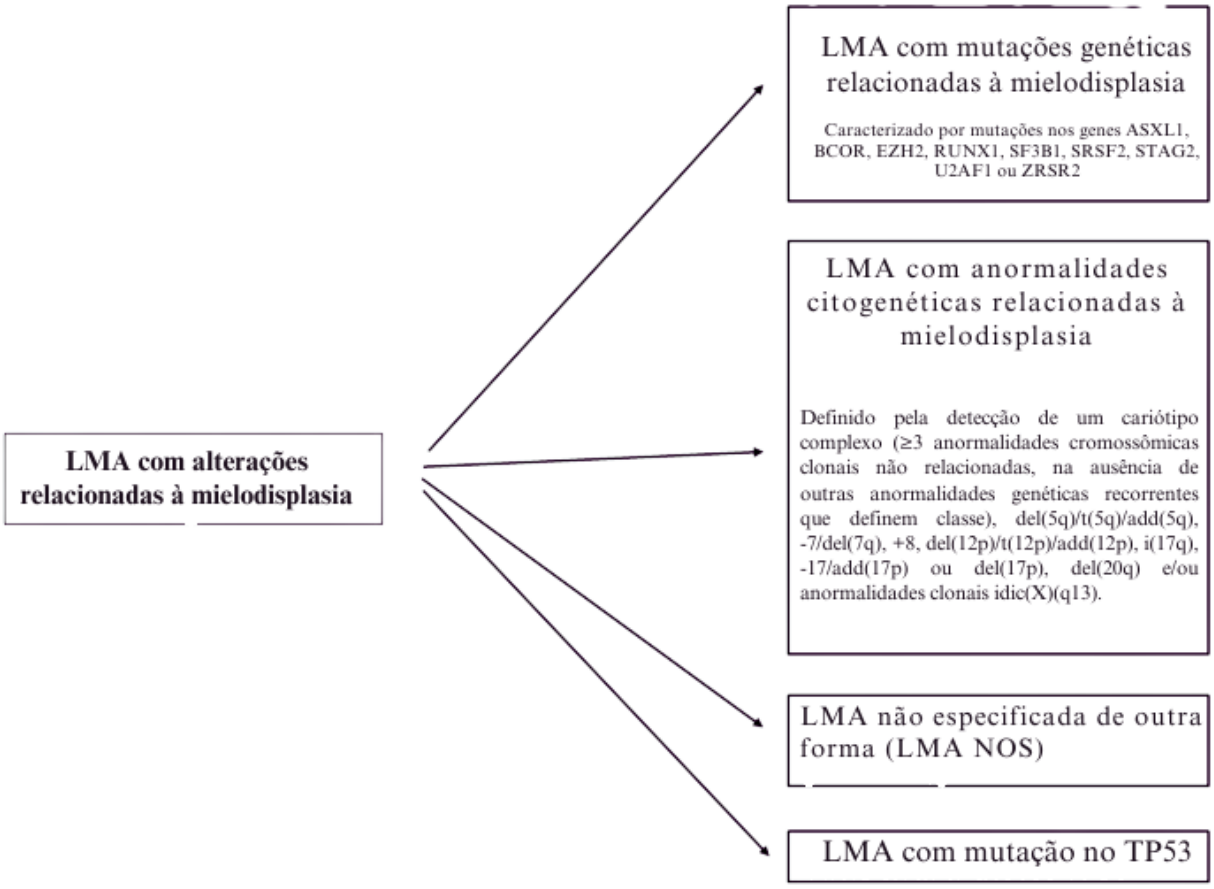


Figura 3. O grupo LMA com alterações relacionadas à mielodisplasia é agora reclassificado como novas categorias de LMA com anormalidades citogenéticas relacionadas à mielodisplasia.
Fonte: Weinberg *et al*., 2023.

I.7 SINTOMAS CLÍNICOS

Os sintomas clínicos de pacientes com LLA está relacionada ao acúmulo de células linfóides malignas e pouco diferenciadas na medula óssea, sangue periférico e locais extramedulares. A apresentação pode ser inespecífica, com uma combinação de sintomas constitucionais e sinais de insuficiência da medula óssea (anemia, trombocitopenia, leucopenia).

Os sintomas mais comuns incluem "sintomas B" (febre, perda de peso, suores noturnos), hemorragia fácil ou nódoas negras, fadiga, dispnéia e infecção. O envolvimento de sítios extramedulares geralmente ocorre e pode causar linfadenopatia, esplenomegalia e hepatomegalia em 20% dos pacientes (Alvarnas *et al*., 2015; Jabbour *et al.*, 2015). O envolvimento do SNC (sistema nervoso central) no momento do diagnóstico ocorre em 5% a 8% dos pacientes e se apresenta mais comumente como déficits de nervos cranianos ou meningismo. A LLA de células T também pode apresentar massa mediastinal (Jabbour *et al*., 2015). Destacando a importância do monitoramento de marcadores hematológicos, por meio

de hemogramas como: glóbulos vermelhos (milhões/mm3), hemoglobinas (g/dL), hematócrito (%), volume corpuscular médio (VCM) em fL, hemoglobina corpuscular média (HCM) em pg, linfócitos (mm^3), plaquetas (mm3) e demais marcadores. E os dados dos exames bioquímicos como: uréia (mg/dL), glicose (mg/dL) e creatinina (mg/dL) e entre outros.

Reconhece-se que a resposta à terapia inicial prediz o resultado. Historicamente, a resposta ao tratamento foi avaliada morfologicamente. Recentemente, tornou-se prática padrão avaliar pacientes com doença residual mínima (DRM) usando técnicas moleculares como citometria de fluxo e PCR -Reação em cadeia da polimerase, em português-(DONGEN et al. 2015). No trabalho de Bruggemann e colaboradores, redefiniram os pacientes de risco padrão para baixo risco, risco intermediário e alto risco com taxas de recaída de 0%, 47% e 94%, respectivamente, com base na persistência de DRM elevado, definido como$>10^{-4}$ (Bruggemann *et al.* 2016).

I.8 PARÂMETROS CLINICOS E FATORES DE PROGNÓSTICO

A avaliação precisa do prognóstico é central para o manejo da LA. A estratificação de risco permite que o médico se oriente ao regime de tratamento inicial mais adequado, bem como quando considerar o transplante alogênico de células-tronco (Allo-SCT). Ao longo tempo a estratificar os pacientes se dá pela a idade e a contagem de glóbulos brancos no momento do diagnóstico. O aumento da idade indica um pior prognóstico. Pacientes com mais de 60 anos têm resultados particularmente ruins, com apenas 10 a 15% de sobrevida em longo prazo (Rowe *et al.*, 2010).

Os idosos tendem a doenças com biologia desfavorável como as comorbidades médicas e incapacidade de tolerar regimes de quimioterapia padrão, deste modo a idade ajuda a orientar a terapia. No entanto, um grande ensaio prospectivo para determinar um melhor tratamento, segundo o protocolo de estudo- MRC UKALL XII / ECOG E2993- encontrou uma significativa diferença de livre doença (LD) e sobrevida global (SG) na idade usando um ponto de corte de 35 em doença Ph-negativo (Filadélfia-negativo). Da mesma forma, eles descobriram que uma contagem elevada de leucócitos no momento do diagnóstico, definida como $>30 \times 10^9$ para B-LLA ou $>100 \times 10^9$ para o T-LLA, era um fator prognóstico independente para LD e SG. Com base nestes resultados, a doença grave pode ser classificada como de baixo risco (sem fatores de risco baseados na idade ou na contagem de leucócitos), risco intermediário (idade >35 ou contagem elevada de leucócitos), ou alto risco (idade >35 e contagem elevada de leucócitos). As taxas de sobrevivência global de 5 anos com base nessas categorias de risco foram de 55, 34 e 5%, respectivamente (Rowe *et al.* 2005).

A investigação diagnóstica da leucemia é um processo complexo, que requer a realização de múltiplos exames para confirmar o diagnóstico e determinar o estágio da doença. Entre os estudos iniciais essenciais estão o hemograma completo, o painel metabólico abrangente, os testes de função hepática (LFTs) e o painel de coagulação. Esses exames são frequentemente complementados pela análise do esfregaço de sangue periférico e pela realização de biópsia e aspiração da medula óssea, procedimentos fundamentais para a confirmação diagnóstica e caracterização da doença (Chennamadhavuni *et al*., 2023).

I.9 CITOGENÉTICAS E LEUCEMIAS AGUDAS

Os fatores clínicos são importantes na orientação da terapia e risco, já as alterações citogenéticas têm um papel significativo na determinação dos riscos e diagnóstico. Diversas mudanças são necessárias para o desenvolvimento do câncer, mas se sabe hoje que anormalidades genéticas estão associadas diretamente com a fisiopatologia da leucemia, desde o descobrimento do cromossomo Filadélfia (Juliusson e Hough, 2016).

Destacando a importância de exames citogenéticos como a cariotipagem por bandeamento, em hospitais e centros de referência no tratamento de leucemias. Uma vez que, a cariotipagem é uma técnica bem consolidada utilizada nessas caracterizações em pacientes adultos com LA, assim como a hibridização in situ fluorescente (FISH) e a reação em cadeia da polimerase com transcrição reversa (RT-PCR) (Gökbuget *et al*., 2024). Apesar de a cariotipagem ser considerada o método padrão-ouro para análise citogenética, ela apresenta limitações na detecção de deleções crípticas e translocações sutis, como a inv(16)(p13.1q22), a fusão PML-RARA e a translocação críptica t(9;22).

Diante dessas limitações, é fundamental informar a equipe de citogenética sobre a possibilidade de tais anormalidades e recomendar a realização de estudos complementares, como a hibridização in situ fluorescente (FISH), para uma avaliação mais precisa (Narayanan *et al.*, 2020). Contudo, embora relativamente mais laboriosa, apresenta uma combinação de menor custo e permite um olhar mais amplo sobre as várias alterações visualizáveis citogeneticamente.

No caso do cromossomo Filadélfia t(9;22), é a alteração com maior impacto no prognóstico e tratamento. A prevalência de t (9; 22) na LLA adulta pode variar de 15 a 50% e aumenta com a idade (Faderl *et al*. 2017). A positividade tem implicações tanto em termos de prognóstico quanto de tratamento. Historicamente, a LLA Ph-positiva tem uma sobrevida em 1 ano de cerca de 10%. No entanto, com o desenvolvimento de TKIs, a sobrevida melhorou e,

deste modo, os status de Ph de todos os pacientes deve ser obtido antes do início da terapia. Análise subsequente do protocolo de estudo MRC UKALL XII / ECOG E2993, foram identificados subgrupos citogenéticos de Ph-negativos com doenças tendo resultados inferiores. Estes incluíram t (4; 11), *KMT2A* translocação, t (8; 14), cariótipo complexo ($\geqslant$ 5 cromossômicos anormalidades) e baixa hipodiploidia (30-39 cromossomos) / triploidia (60-78 cromossomos). Entretanto, pacientes com hiperdiploidia e del (9p) teve um resultado significativamente melhor (Moorman *et al*. 2007).

Em um estudo posterior, o *Southwest Oncology Group* (SWOG) mostrou que entre os 200 pacientes do estudo, o perfil citogenético foi um fator prognóstico mais importante do que idade ou contagem de leucócitos (Pullarkat *et al.* 2008). A pouco tempo, um subgrupo de LLA de alto risco sem t (9; 22) foi identificado com um perfil genético similar ao da LLA Ph-positiva. Sendo chamada de"*Ph-like"* ALL tem sido associado com uma baixa resposta à quimioterapia de indução, doença residual mínima elevada e baixa taxa de sobrevivência (Roberts *et al.* 2014; Faderl *et al*. 2017).

Com o conhecimento atual, os fatores prognósticos em adultos com LLA da National Comprehensive Cancer Network (NCCN) desenvolveram recomendações para abordar a estratificação de risco (Alvarnas *et al.* 2015). O Institutos Nacionais de Câncer define que os adolescentes e adultos jovens (AJA) para aqueles com idades entre 15 e 39 anos. O NCCN reconhece que AJA pode se beneficiar do tratamento com regimes inspirados em pediatria e, portanto, são considerados separadamente dos adultos >40 anos (Huguet *et al.* 2003; Stock *et al.*, 2008). Ambas as faixas etárias são então estratificadas em alto risco para subgrupos de Ph-negativos de risco padrão. O subgrupo Ph negativo pode ainda ser categorizado como de alto risco com base na presença de MRD, leucócitos elevados ou citogenética desfavorável, como já mencionado.

Em relação a LMA, o perfil citogenético (cariótipo normal ou alterações cromossômicas) continua sendo o indicador prognóstico mais importante na LMA, permitindo a estratificação dos pacientes em grupos de risco favorável, intermediário e adverso. O grupo de risco favorável inclui a leucemia promielocítica aguda (representada por t(15;17)) e a leucemia mieloide aguda com fator de ligação ao núcleo (LMA-CBF), que abrange grupos citogenéticos como t(8;21), inv(16) e t(16;16). Por outro lado, cariótipo complexo e outras anormalidades citogenéticas e moleculares estão associadas a piores resultados de tratamento e sobrevivência (Chung et al., 2017). Na leucemia mieloide aguda

com carióto normal ou citogeneticamente normal representa quase metade de todos os casos de LMA, é classificada como de risco intermediário (Vardiman *et al.,* 2002; NCCN 2016).

Além disso, o prognóstico favorável relacionado às mutações CEBPA pode estar limitado à variante bialélica, e não à monoalélica, conforme indicado por uma recente meta-análise (Li et al., 2015). Além disso, mutações KIT em pacientes com CBF-AML, especialmente t(8;21), estão associadas a um prognóstico pior. Essa estratificação é importante, pois apesar do uso de quimioterapia intensiva e transplante de células-tronco hematopoéticas (HSCT), metade dos pacientes jovens (menores de 60 anos) e 80% dos pacientes com mais de 60 anos enfrentam falhas no tratamento, recaídas ou complicações decorrentes do tratamento (Burnett *et al*., 2011).

As opções de tratamento para LMA, principalmente o transplante alogênico de células-tronco (HSCT), continuam a ser determinadas pela citogenética (ou seja, anormalidades cromossômicas), biomarcadores moleculares e a avaliação da remissão morfológica (Döhner *et al*., 2010; Cornelissen *et al*., 2012). Pacientes com doenças de alto risco geralmente são submetidos a transplante de células-tronco, enquanto aqueles com doenças de baixo risco geralmente não passam pelo procedimento. No entanto, o papel do transplante em pacientes com LMA citogeneticamente normal permanece incerto. Pacientes com mutações no gene *NPM1*, mas sem o genótipo *FLT3-ITD*, apresentam um prognóstico relativamente melhor em comparação com aqueles que possuem mutações *FLT3-ITD* concomitantes, e, por isso, não são mais recomendados para transplante durante a sua primeira remissão completa (NCCN 2016).

Além disso, é importante destacar que já foi demonstrada que o perfil das populações da Amazônia brasileira é distinto de outras populações da África, Europa, Américas e do Sul e Leste da Ásia, uma vez que é formado por um alto grau de miscigenação (de Carvalho *et al*., 2020).

I.10 INSTABILIDADE CROMOSSÔMICA EM PACIENTES COM LA

A aneuploidia pode influenciar o desenvolvimento tumoral, mas se esse impacto é positivo ou negativo depende do tipo de célula e do contexto genético (Holland *et al*., 2009). A instabilidade cromossômica (INC) refere-se à taxa crescente com que as células adquirem novas alterações cromossômicas. Dependendo do tipo de anormalidade, a INC pode ser classificada como numérica (nINC), caracterizada por ganhos e perdas de cromossomos, e

estrutural (e INC), representada por translocações cromossômicas e deleções (Bakhoum *et al*., 2014).

Evidências mostram que a aneuploidia e a INC iniciam um ciclo vicioso que gera instabilidade genética e cariotípica. Observações clínicas e experimentais vinculam essas alterações à progressão do câncer, sugerindo que a aneuploidia e a INC contribuem para a evolução tumoral ao gerar instabilidade genômica e heterogeneidade intratumoral, características marcantes do câncer (Targa *et al*., 2018). Pesquisas recentes têm demonstrado uma relação profunda entre a INC e a origem, progressão e recidiva de diversos tipos de câncer (Bakhoum *et al*., 2018; Lee *et al*., 2011; Bach *et al*., 2019; Salgueiro *et al*., 2020).

A INC atua não apenas como um mecanismo promotor de tumor, mas também como um mecanismo supressor. Isso é evidenciado pelo fato de que diferentes níveis de INC resultam em desfechos distintos. Níveis moderados ou baixos de INC estão associados a taxas mais altas de características genéticas que promovem o câncer. Em contrapartida, níveis extremos de INC podem reduzir a aptidão celular ou induzir apoptose (Silk *et al.*, 2013). Entretanto, a INC pode ser potencialmente oncogênica, mas níveis específicos de INC podem ter efeitos contrastantes em diferentes tecidos (Hoevenaar *et al*., 2020).

Esses mecanismos de INC e suas assinaturas podem ser amplamente observados na leucemia mieloide aguda (LMA), uma doença heterogênea caracterizada pela proliferação e acúmulo anormais de células precursoras mieloides na medula óssea (Estey *et al*., 2006). As anormalidades citogenéticas na LMA são um fator prognóstico crucial, utilizadas tanto para a estratificação de risco quanto para a orientação das estratégias de tratamento (Grimwade *et al*., 2011; Döhner *et al*., 2017). Neste caso, um cariótipo complexo (CK) está associado a um prognóstico ruim (Jin et al., 2020). Em pacientes mais velhos (≥60 anos), apenas 10–44% daqueles com ≥3 anormalidades citogenéticas alcançam remissão completa (RC) após a terapia. Para aqueles com ≥5 anormalidades cromossômicas, as taxas de RC são ainda menores, variando entre 7–26% (Van *et al*., 2007; Mrózek *et al*., 2008).

Anormalidades cromossômicas e genéticas desempenham um papel significativo na diferenciação patológica e proliferação de células precursoras linfoides. A leucemia linfoblástica aguda é composta por vários subtipos genéticos distintos, caracterizados por alterações moleculares, como aneuploidia, rearranjos cromossômicos, alterações no número de cópias de DNA e mutações de sequência (Kimura *et al.*, 2020). No caso da hiperdiploidia alta (51–65 cromossomos) está presente em 10% dos adultos com LLA (Inaba *et al*., 2020).

Estudos mostram que crianças com LLA e hiperdiploidia alta respondem bem aos regimes de quimioterapia padrão e apresentam melhores resultados de tratamento em comparação com pacientes pediátricos não hiperdiploides (Moorman *et al*., 2010). A hiperdiploidia baixa ocorre em cerca de 10-11% das crianças e 10-15% dos adultos com leucemia linfoblástica aguda (Mrózek *et al.,* 2004). Sua incidência aumenta com a idade e, diferentemente da hiperdiploidia alta, está associada a um prognóstico desfavorável. Estudos indicam que pacientes com hiperdiploidia baixa têm um período de sobrevida mais curto (Braoudaki *et al*., 2012).

O cariótipo hipodiploide é observado em menos de 7% das crianças e adultos com LLA-B, e é uma anomalia citogenética rara na LLA. A hipodiploidia pode ser classificada em três subtipos: quase haploidia, com 24-31 cromossomos; baixa hipodiploidia, com 32-39 cromossomos; e alta hipodiploidia, com 40-44 cromossomos (Creasey *et al*., 2021; Safavi *et al*., 2017). Observou-se que a LLA quase haploide e a LLA hipodiploide baixa diferem em seus perfis mutacionais. Além disso, sugere-se que casos de LLA com alta hipodiploidia podem apresentar instabilidade cromossômica (Safavi *et al*., 2015).

Devido aos maus resultados do tratamento, ainda se buscam novos regimes terapêuticos para pacientes com LLA hipodiploide. Ainda não está claro se o transplante de células-tronco hematopoiéticas durante a primeira remissão completa (CR1) é benéfico (McNeer *et al*., 2019). Embora a CIN seja amplamente presente em diversos tipos de câncer aneuploides e tenha relevância clínica, sua presença na leucemia linfoblástica aguda de células B (LLA-B) ainda é amplamente inexplorada (Molina *et al*., 2024). Principalmente quando avaliamos o papel da instabilidade cromossômica em pacientes adultos com LLA.

II. OBJETIVO PRINCIPAL

Descrever o perfil citogenético dos pacientes adultos com leucemia linfoblástica aguda (LLA) e leucemia mieloide aguda (LMA), associando a alterações hematológicas e bioquímicas.

II.1 Objetivo secundário

a) Descrever as alterações citogenéticas dos pacientes adultos com LLA e LMA tratados na região norte do Brasil.

b) Associar as alterações citogenéticas com alterações bioquímicas e hematológicas de dados clínicos dos pacientes com LLA e LMA.

c) Relacionar as alterações bioquímicas e hematológicas de dados clínicos dos pacientes com LLA com cariótipo normal e sexo dos pacientes com LA.

d) Descrever e caracterizar instabilidade cromossômica em pacientes adultos com LLA e LMA.

CAPÍTULO 1. CARACTERÍSTICAS HEMATOLÓGICAS E BIOQUÍMICAS ASSOCIADAS A ALTERAÇÕES CITOGENÉTICAS EM PACIENTES ADULTOS COM LEUCEMIA LINFOBLÁSTICA AGUDA (LLA) DA REGIÃO NORTE DO BRASIL

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MDPI

Article

Hematological and Biochemical Characteristics Associated with Cytogenetic Findern Alterations in Adult Patients with Acute Lymphoblastic Leukemia (ALL) from the Northern Region of Brazil

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Citation: Duarte, D.d.S.; Teixeira, E.B.; de Oliveira, M.B.; Carneiro, T.X.; Leão, L.B.C.; Mello Júnior, F.A.R.; Carneiro, D.M.; Nunes, P.F.; Cohen-Paes, A.d.N.; Alcantara, D.D.F.Á.; et al. Hematological and Biochemical Characteristics Associated with Cytogenetic Findern Alterations in Adult Patients with Acute Lymphoblastic Leukemia (ALL) from the Northern Region of Brazil. *Biomedicines* **2024**, *12*, x. https://doi.org/10.3390/xxxxx

Academic Editor: Jehan J. El-Jawhari

Received: 12 April 2024
Revised: 7 May 2024
Accepted: 8 May 2024
Published: date

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Abstract: Acute lymphoblastic leukemia (ALL) is an aggressive neoplasm derived from B and/or T cell lineage (B-ALL; T-ALL). For the first time, this study describes, cytogenetically, the karyotypic alterations in adults with ALL in the northern region of Brazil and their relationship with hematological and biochemical characteristics. Through banding analyses,

immunophenotyping, as well as hematological and biochemical examination data obtained directly from patients' records, we found that chromosome 21 aneuploidy was the most frequent. The cytogenetic structural alterations observed with the highest incidence among the patients were: t(9;22), t(4;11), t(1;19), del(6q), and del(9p). In patients presenting with chromosome alterations, we verified that patients with t(4;11) have elevated red blood cell levels and patients with del(9p) presented with distinct and high values of hematological parameters compared to other patients. Regarding biochemical alterations, we observed that patients with translocations (4;11) and del(6q) presented with elevated urea levels compared to other patients, highlighting its relationship to kidney changes and patient prognosis. Thus, our study highlights that variations in hematological and biochemical data are associated with specific cytogenetic changes and other factors, which may impact the prognosis of adult patients with ALL.

Keywords: acute lymphoblastic leukemia; hematological characteristics; biochemical
characteristics; chromosome 21 aneuploidy; t(9;22); t(4;11); t(1;19); del(6q); del(9p)

1. Introduction

Acute lymphoblastic leukemia (ALL) is an aggressive neoplasm derived from B and/or T cell lineage (B-ALL; T-ALL), affecting immature lymphocytic cells in the blood [1]. Adult patients have an incidence of 1 per 100 inhabitants, with the incidence being higher in elderly adults, with a survival decrease related to age advancement [2]. According to the WHO, ALL is characterized mainly by cytogenetic alterations that lead to leukemogenesis [1,3]. Karyotyping is a well-consolidated technique used in these characterizations in adult patients with ALL, as well as fluorescence in situ hybridization (FISH) and reverse transcription polymerase chain reaction (RT-PCR) [4]. Therefore, mapping these changes through genetic and molecular tests is, nowadays, mandatory in the prognosis and risk stratification of patients [5], as well as highlighting the molecular epidemiology of a distinct geographic region. Thus, our study describes, for the first time, cytogenetically, the karyotype alterations in adults with ALL in the northern region of Brazil, and the relationships with hematological, biochemical, and other molecular characteristics in these patients.

2. Materials and Methods

2.1. Ethical Aspects and Patients

This study was approved by the Ethics Committee of Ophir Loyola Hospital, Belém-Pará (number: 4,409,317). The cohort comprised 45 adult patients of both sexes, being represented by 29 men and 16 females, aged over 18 years (mean 34.71 years, SD = 12,818), diagnosed with acute lymphoblastic leukemia of lineage B and T. Patients were from Ophir Loyola Hospital, a reference hospital in the Para state, Brazil. The exclusion criterion was patients with a suggestive or inconclusive diagnosis for ALL. Furthermore, it is worth noting that it has already been demonstrated that the profile of the Brazilian Amazon populations is distinct from other populations in Africa, Europe, the Americas, and

South and East Asia, as it is formed through a high degree of miscegenation [6].

2.2. Cytogenetic Characterization

Blood and marrow samples were collected in heparin tubes and transferred to tubes with MarrowMAX™ from Gibco® (Thermo, Grand Island, NY, USA). Samples were collected after 24 h of culture and 0.1 mL of colchicine was added 2 hours after each collection. They were subsequently centrifuged (1000 rpm for 10 min), the supernatant was removed, and hypotonization treatment started with potassium chloride (KCl) at a concentration of 0.075 M at 37 °C for 20 min. Samples were centrifuged and fixed three times with methanol/acetic acid (3:1). Cell suspensions were placed on histological slides, and then the GTG banding technique was performed [7,8]. Chromosome classification followed the standards of the International Human Cytogenetic Nomenclature System [9]. Twenty metaphases from each of the patients were analyzed. Such data are available in Supplementary Table S1.

2.3. Clinical Data and Biochemical and Hematological Exams

The hematological and biochemical parameters evaluated in this study were collected directly from the medical records of patients with a confirmed diagnosis of ALL, through immunophenotyping. These parameters were evaluated and are available in Table 1. As well as parameters such as sex, lineage, occurrence of death, symptoms presented, and clinical risk were obtained from medical record data.

Table 1. Hematological and biochemical clinical parameters.

Hematological Parameters	Biochemical Parameters
Red cells (million/mm^3)	Urea (mg/dL)
Hemoglobin (g/dL)	Transaminase (AST)/(U/L)
Hematocrit (%)	Creatine (mg/dL)
Mean corpuscular volume MCV (fL)	Glucose (mg/dL)
Mean corpuscular hemoglobin (pg)	Magnesium (mg/dL)
Mean corpuscular hemoglobin concentration (g/dL)	Potassium (mEq/L)
RDW (%)	Sodium (mEq/L)
Leukocytes (mm^3)	
Lymphocytes (relative value)/%	
Lymphocytes (absolute value)/(mm^3)	
Monocyte (relative value)/%	
Monocyte (absolute value)/(uL)	
Neutrophil (relative value)/(%)	
Neutrophil (absolute value)/(mm^3)	
Eosinophil (relative value)/%	
Eosinophil (absolute value)/(µL)	
Basophils (relative value)/%	
Basophils (absolute value)/(uL)	
Rods (relative value)/(%)	
Rods (absolute value)/(ml/µL)	
Platelets (mm^3)	

2.4. Symptom Classification

For this analysis, patients were classified into two groups according to the initial symptoms reported in their medical records when they

were seen at the Ophir Loyola Hospital. The non-hematological group consisted of patients who reported symptoms such as asthenia, bone pain, weakness, and abdominal pain, while the hematological group had initial symptoms such as anemia, thrombocythemia, fever, and lymphomegaly. Also, we checked whether clinical symptoms were associated with hematological and biochemical changes.

2.5. Statistical Analysis

Calculations were performed using the Chicago software, SPSS Inc. (SPSS Inc., released 2008, SPSS Statistics for Windows, Version 17.0). Analyses were performed using Levene's test for distribution analyses and Student's t tests. Group data are expressed as mean ± standard deviation (SD). Nominal values were analyzed with the Fisher's exact test and Odds Ratio. Values of $p \leq 0.05$ were considered significant.

3. Results

3.1. Cytogenetic

The cytogenetic structural alterations observed with the highest incidence among the patients were: t(9;22), t(4;11), t(1;19), del(6q), and del(9p). However, of the 45 karyotypes evaluated, 6 had a normal karyotype (Figure 1).

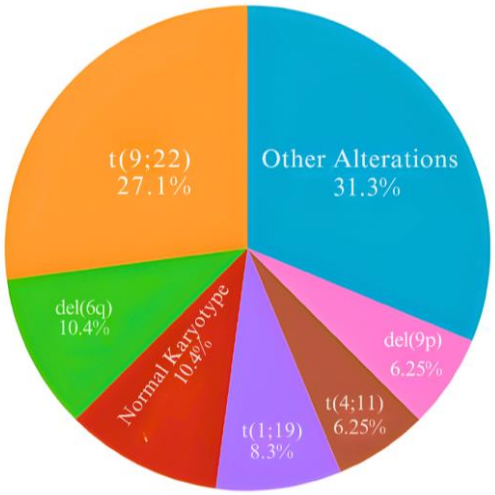

Figure 1. Percentage of cytogenetic alterations and normal karyotype in 46 adult patients with ALL. The other alterations are described in Supplementary Table S1.

Among the aneuploidies observed in this study, chromosome 21 was the most frequent aneuploidy among patients with ALL. Also, monosomies were found involving chromosomes −7, −13 and −17. Triploidies of chromosomes +4, +8, +14, +18 were observed too (Figure 2).

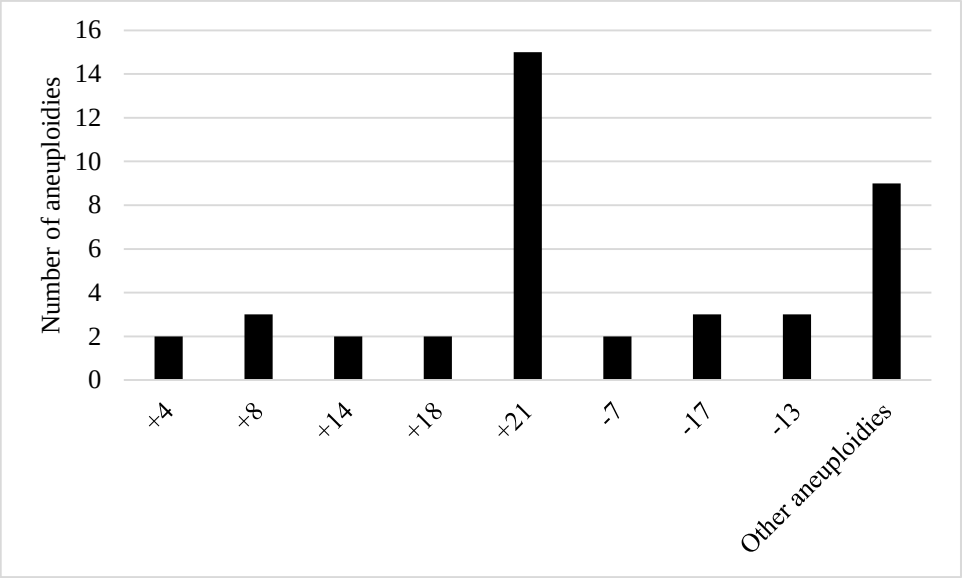

Figure 2. Number of aneuploidies described in 46 patients with ALL.

3.2. Cytogenetic Alterations and Hematological Data

The study evaluated the hematological parameters of adult patients diagnosed with ALL. It was observed that patients who presented the t(4;11) chromosomal translocation had a lower number of red blood cells when compared to other translocations, with mean values of 2.16 (SD = 0.310) and with a *p*-value of 0.047. Patients who had del9p had lower hemoglobin levels (mean = 11.766 g/dL, SD = 2.395) and hematocrit levels (mean = 35.666%, SD = 7.115) compared to the other group with chromosomal abnormalities, with *p* values of 0.035 and 0.035, respectively. However, the mean corpuscular volume (MCV) was higher, with a mean difference of 13.242 fL compared with the other patients with ALL (p = 0.005; SD = 6.097). The mean corpuscular hemoglobin (HCM) was also higher with a difference of 4.246 pg vs. the other patients (p = 0.001; SD = 2.06). All results are shown in Table 2.

Table 2. Hematological clinical exam data.

	Hematological Parameters	Categories	Mean	Min. Value	Max. Value	SD	*p-Value*
t(4;11)	Red cells (millions/mm^3)	t(4;11)	2.163	1.86	2.48	0.310	0.047
		Other	3.081	1.02	4.93	0.765	
	Hemoglobin (g/dL)	del9p	11.766	7.7	15.4	3.955	0.035
		Other	8.597	5.3	15.6	2.333	
	Hematocrit (%)	del9p	35.666	23.7	44.9	10.861	0.035
		Other	26.133	8.7	45.8	7.115	
del(9p)	Mean corpuscular volume MCV (fL)	del9p	100.73	95.18	107.26	6.097	0.005
		Other	87.494	74.01	104.65	7.481	
	Mean corpuscular hemoglobin (pg)	del9p	33.030	30.92	34.66	1.915	0.001
		Other	28.783	23.5	34.66	2.061	
Normal karyotype	Lymphocytes (mm^3)	Normal karyotype	1.950	113.4	1185.8	1.560	0.001
		Other	8.003	324.8	5901.3	8.263	
	Platelets (mm^3)	Normal karyotype	48.571	12	130	43.181	0.001
		Other	142.78	4	396	125.44	
Sex	Red cells (millions/mm^3)	Male	3.214	1.89	4.93	0.7432	0.022
		Female	2.666	1.02	3.58	0.7322	
	Hemoglobin (g/dL)	Male	9.358	5.3	15.6	2.517	0.049
		Female	7.812	2.9	11.6	2.317	
	Hematocrit (%)	Male	28.737	15.7	45.8	7.367	0.018
		Female	23.200	8.7	33.7	6.975	

The values g/dL = grams per liter; mm^3 = cubic millimeter; Fl = fentoliter; pg = picograms.

Patients with ALL and normal karyotype present with smaller amounts of lymphocytes compared to other patients, with a mean value of 1950 m/mm^3 (p = 0.001; SD = 1.56). The mean platelet values, with a mean value equal to 48.571, are lower compared to the other patients with ALL (p = 0.001; SD = 43.181). Among the patients evaluated, 26 were male and 16 were female. Male ALL patients had a higher amount of red blood cells (p = 0.022; SD = 0.732), hemoglobin (p = 0.049; SD = 2.517), and hematocrit (p= 0.018; SD = 7.367), with significant mean differences in relation to women (Table 2).

3.3. Cytogenetic Alterations and Biochemical Data

Our study also evaluated changes in biochemical parameters in adult patients with ALL. The patients with ALL with t(4;11) translocations had high mean values of urea, when compared to other patients with ALL; mean equal to 145.66 mg/dL (p = 0.005; SD = 53.758). Also, patients with ALL and del6q showed high mean values of urea in relation to the patients evaluated in this study, having a mean value of 109 mg/dL (p= 0.031; SD = 116.404). Furthermore, the amount of glucose observed in patients with ALL and initial hematologic symptoms was higher compared to other patients. In addition, the amount of glucose observed in patients with ALL and initial symptoms (non-hematological) was lower than other patients, with a mean equal to 101,875mg/dL (p = 0.027; SD = 25.723). Additionally, male patients with ALL had an elevated amount of creatinine compared to females, with a

mean difference of 6686mg/dL (p = 0.041; SD = 12.43). All data are available in Table 3.

Table 3. Biochemical clinical exam data.

	Parameters	Categories	Mean	Min. Value	Max. Value	SD	*p*-Value
t(4;11)	Urea (mg/dL)	t(4;11)	145.66	80	232	78.08	0.005
		Others	48.57	15	294	53.79	
del(6q)	Urea (mg/dL)	del(6q)	109	19	294	116.4	0.031
		Others	48.3	13	157	47.09	
Initial symptoms	Glucose (mg/dL)	Non-hematological	101.87	69	164	25.72	0.027
		Hematological	140.4	101	207	47.17	
Sex	Creatine (mg/dL)	Male	90.55	0.54	6.23	124.3	0.041
		Female	23.69	0.3	2.4	32.8	

The values mg/dL = Milligrams per deciliter.

4. Discussion

4.1. Cytogenetic Abnormalities

Our study characterizes cytogenetic changes in the abnormal karyotype in adult patients in the northern region of Brazil and demonstrates how such karyotypes and other factors can be associated with changes in hematological and biochemical values. Notably, karyotyping promotes the detection of recurrent chromosomal rearrangements, being a tool used in the management and risk stratification of adult patients with ALL, in addition to immunophenotyping and molecular diagnosis [1;3].

In the present study, chromosome 21 trisomy was the most common aneuploidy in patients with ALL (Figure 2). These phenomena were observed even in of high hyperdiploid and hypodiploid cases and also in almost all haploid cases of ALL [10]. The relationship between chromosome 21 and ALL can be reinforced by the fact that individuals with Down syndrome have a greater risk of developing B-ALL [11,12]. Furthermore, patients with iAMP21-ALL, an amplification in this chromosome, are classified as high risk and at risk of adverse responses to intensive chemotherapy [13,14].

The t(9;22) translocation was the most common structural alteration among patients with ALL, present in 27.1% of the patients in this study (Figure 1). Therefore, the prevalence of *BCR::ABL* in other countries presents a percentual mean of 28% (SD = 7%) and increases with the age of patients with ALL [14–21]. The Ph (Philadelphia) chromosome is formed from a translocation between chromosomes 9 and 22, generating a fusion gene involving the 5′ region of *BCR* fused to the 3′ sequences of *ABL1* [22], a well-established modification in oncohematology. This finding directly points to the treatment strategy, for example, the addition of *BCR::ABL1* tyrosine kinase inhibitors (TKIs) to intensive chemotherapy has significantly improved outcomes for patients with

Philadelphia chromosome-positive (Ph+) ALL. Recently, chemotherapy-free regimens with blinatumomab and TKIs have shown excellent results at the forefront and may signal an emerging paradigm shift in the management of Ph+ ALL [23–25]. In fact, the use of TKIs in treatment has significantly increased the rates of complete remission of ALL. Thus, we highlight the importance of t(9;22) in the diagnosis by cytogenetic tests in managing patients with ALL.

We observed that the t(1;19) translocation is present in 8.33% of patients with ALL. The *TCF3::PBX1* gene is the third most prevalent recurrent chromosomal translocation and, worldwide, presents a percentual mean of 6% (SD = 3.1%) [14,21,26–29]. Such a translocation results in a hybrid protein as a consequence of *TCF3::PBX1* fusion. These differences in outcome between patients who were positive and negative for the *TCF3::PBX1* gene have been described in ALL [30–33]. Given that studies associate it with a good prognosis, depending on the age group [29,34], patients may also have an intermediate prognosis [35,36] and an unfavorable prognosis [37,38].

In our study, 6.25% of the patients evaluated presented with the t(4;11) translocation. The t(4;11)/*KMT2A::AFF1* translocation is present at a percentage mean of 5.1% (SD = 2.41) of non-Philadelphia adult cases with B cell precursors [18,20,21,27,28,39]. Such translocations occur in B-type precursor cells and is characterized by a higher leukocyte count compared to other ALL subtypes and an immature phenotype, in most cases with a lack of CD10 expression in leukemic cells [39,40]. It is associated with a poor prognosis for ALL patients, as well as a higher risk of relapse [41–43]. Thus, the role of alloHSCT in the treatment of t(4;11) BCP-ALL is corroborated. Having an impact on the pre-transplant MRD status, this highlights the need for additional therapeutic intervention and prospective clinical trials focused on this patient population, with the aim of reducing the tumor burden before transplantation and decreasing the risk of relapse after alloHSCT [44].

Furthermore, we observed del(9p) in 6.25% of ALL patients. This alteration was observed in about 9% of cases of acute lymphoblastic leukemia in adults [45]. An important target of deletion of the chromosomal region 9p is the *CDKN2A*, a gene that encodes p16 (*INK4a*) and p14 (*ARF*). Plus, contiguous genes such as *CDKN2B*, which encodes p15 (*INK4b*), or *MTAP*, which encodes methylthioadenosine phosphorylase, can be included in the deletions, and such deletions are also strongly correlated with changes in *PAX5* genes [46,47]. The deleted *CDKN2* gene was frequently observed throughout ALL progression and is considered an unfavorable prognostic marker in long-term outcomes [48]. Studies also show that the *CDKN2* deletion is frequently acquired during the progression of Ph-positive ALL (Philadelphia positive), serving as a poor prognostic marker of long-term outcome in patients with Ph-positive ALL with *CDKN2A* deletion, even after treatment with second-generation tyrosine kinase inhibitors [49].

The del(6q) cytogenetic alteration was present in 10.4% of patients with ALL. They are a recurrent cytogenetic alteration in ALL. The frequency of del(6q) was found to be in the described proportion of 10.1% patients with ALL [50]. This corroborates several studies using *FISH* and a loss of heterozygosity (LOH), which demonstrated several common regions of deletion involving 6q21–q23 [51]. Furthermore, 6q deletions are associated with an intermediate or poor prognostic outcome in adults [52]. The deletion of the long arm of chromosome 6 in

ALL patients typically occurs in the region of the *GRIK2* gene most often affected by 6q16 deletions; complete or partial loss of *GRIK2* function may contribute to some of the lymphoid leukemia proliferations [53,54]. In the case of del6q in T-ALL, it was described through genomic analysis and functional models that co-deletion of two contiguous genes on 6q14 increases malignancy through dysregulation of the ribosome–mitochondria axis, suggesting the potential for therapeutic intervention [55].

Among the ALL patients, 10.4% did not present any cytogenetic alterations. This profile is associated with an intermediate prognosis [56]. Normal karyotypes have been observed in approximately 22% of acute lymphoblastic leukemia cases in adults and children [39]. ALL patients with unaltered karyotypes could receive the same prognostic evaluation as ALL patients with *BCR::ABL1*+. For a better prognosis of these patients, allogeneic hematopoietic stem cell transplantation (alloHSCT) should be actively performed [57].

4.2. Hematological Modifications

Our study observed that patients with ALL and t(4;11) showed significant differences in the count of red blood cells compared to ALL patients with other cytogenetic changes and with a normal karyotype ($p = 0.47$) (Table 2). The chimeric product *MLL-AF4* or *KMT2A*/*AFF1* binds and deregulates the expression of essential target genes involved in lymphocyte differentiation, including the homeobox A cluster genes *HOXA* and *MEIS1* [58]. Overexpression of *HOXA* inhibits erythropoiesis and megakaryopoiesis, resulting in decreased hemoglobin levels and platelet counts (Figure 3) [59]. The patients in the present study had red blood cell levels below the normal level in healthy adults [60]. Further, Zhang and his collaborators described acute myeloid leukemia patients presenting with t(4;11) had the simultaneous occurrence of anemia and thrombopenia [61], pointing to the influence of this genetic alteration on red blood cell count.

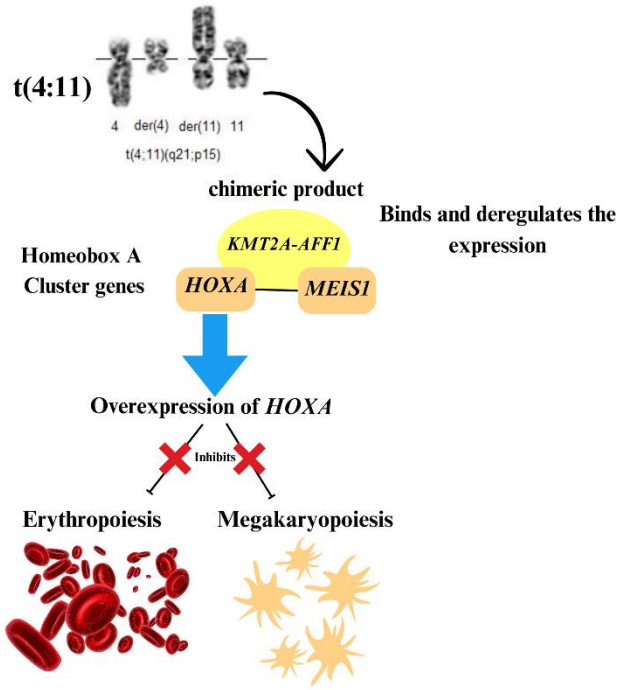

Figure 3. Schematic representation of the biomechanisms related to t(4;11) and the reduction of hematological cells. The image of the cytogenetic translocation was obtained from the *Atlas of Genetics and Cytogenetics in Oncology and Haematology* [62].

Patients with ALL and del(9p) showed significant differences in terms of mean hemoglobin (p = 0.035), hematocrit (p = 0.035), mean corpuscular volume (MCV) (p= 0.005), and mean corpuscular hemoglobin (MCH) values (p = 0.001), compared to other patients with ALL. The del(9p)-associated loss of the *CDKN2A/B* gene may directly contribute to leukemogenesis [63,64]. There is a report of a patient with ALL and del(9p), where the patient did not respond to chemotherapy treatment and died within one week of induction of chemotherapy (HyperCVAD-A), presenting with symptoms of anemia and thrombopenia [65]. Furthermore, patients with AML and del9p, with a loss of the *CDKN2A* gene, presented with hemoglobin values like those observed in our study [66]. Anemia is also classified according to the MCV value, as microcytic (decreased MCV), normocytic (normal MCV) or macrocytic (increased MCV) [67,68]. The combination of MCV and red blood cell distribution allows for further sub-classification of hematological diseases [69]. This fact highlights the importance of monitoring these parameters in leukemia patients with del(9p).

We observed that patients with ALL and a normal karyotype showed a significant reduction in the average number of lymphocytes and platelets compared to other patients with ALL (p = 0.001). Karyotypically normal patients have presented lymphocyte and platelet levels lower than the standards of healthy individuals [60]. It is important to note that, traditionally, white blood cell count, age, and sex are used to this day in patient risk stratification [70,71]. Therefore, these patients are associated with an unfavorable prognosis throughout treatment [57].

In the present study, female patients with ALL showed a significant reduction in the number of red blood cells (p = 0.022), hemoglobin (p = 0.049), and hematocrit (p = 0.018) compared to male patients (Table 1); however, both sexes of patients with ALL had mean amounts of red blood cells, hemoglobin, and hematocrit below the limits considered normal in both sexes [60]. Nevertheless, studies in patients with AML have observed an association between increasing age and being male and a decrease in red blood cell count [72]. It should be noted that changes in red blood cells are related to the development of anemia [68].

4.3. Biochemical Alterations

Patients with ALL with cytogenetic alterations of the del(6q) and t(4;11) type had high mean urea values compared to other patients with ALL (Table 3). Studies show that del(6q) is associated with the development of focal segmental glomerulosclerosis causing dysregulation of VEGF (vascular endothelial growth factor) synthesis caused by the deletion of the E2F3 gene (Figure 4) [73]. In both cytogenetic alterations, the amount of urea is above the values considered standard in biochemical tests [74]. The amount of urea is used to assess kidney function, in addition to the body's nitrogen balance being controlled by regulating urea generation [75]. Acute renal failure has already been observed in patients with ALL at the time of diagnosis [76,77], where the incidence rate of renal failure in patients with untreated ALL ranges from 13% to 25% [78,79]. In this way, renal infiltration is related to a poor prognosis in patients with ALL [80]. However, we highlight the need for more studies related to t(4:11) and urea levels, since we did not observe studies associating both.

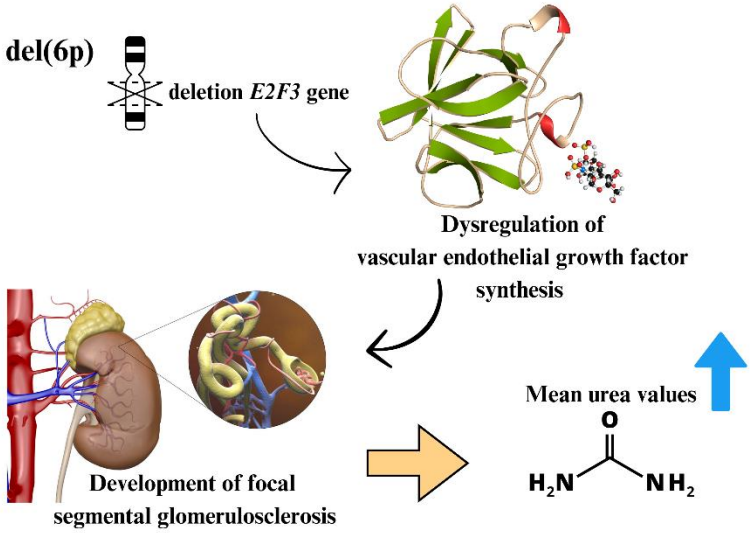

Figure 4. Schematic representation of the biomechanisms related to del(6p) and the increase in urea levels.

Patients with ALL who presented with initial hematological symptoms such as anemia and thrombocytopenia, showed increased glucose levels with significant differences in relation to other patients who did not present these characteristics. In leukemia, oncogenic driver genes such as *MYC* and *RAS* alter metabolic pathways. In ALL, *MYC* leads to increased glucose uptake and glycolytic activity, glutaminolysis,

and lipid synthesis [81–84]. Changes in anabolic metabolism through *RAS* mutations increase glucose uptake and the expression of glycolytic enzymes [85,86]. Such alterations in these oncogenes could explain the high glucose levels observed in the ALL patients evaluated. We observed significant differences between the sexes of patients in relation to creatinine values (p = 0.041). In both sexes, patients had creatinine values below what is considered normal when compared to standard values [73]. Patients with ALL and alterations in creatinine levels have already been reported, mainly presenting kidney damage caused by hematological diseases [78,87].

5. Conclusions

Our study is the first to describe cytogenetic changes and karyotypes in adult patients with acute lymphoblastic leukemia (ALL) in this admixture adult population in the north of Brazil. We observed that the t(1;19) alteration is described at a higher frequency compared to the world mean. Furthermore, we noted that cytogenetic changes, sex, and initial symptoms of the disease may be linked to variations in hematological and biochemical characteristics in patients with ALL. Regarding changes, we mainly observed that the 6q deletion can lead to kidney damage. Therefore, hematological and biochemical changes associated with cytogenetic findings can help predict prognostic aspects of adult patients with ALL.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1.

Author Contributions: D.d.S.D., R.M.R.B., and A.S.K. conceptualized the study and designed the research. D.d.S.D., E.B.T., A.S.K., and R.M.R.B. performed the research. T.X.C., L.B.C.L., F.A.R.M.J., D.M.C., and P.F.N. analyzed the data. D.d.S.D., E.B.T., M.B.d.O., and A.S.K. wrote the paper. D.D.F.Á.A., A.C.-P., R.M.R.B., E.B.T., M.B.d.O., F.A.R.M.J., D.d.S.D., and A.C.-P. contributed to scientific discussion, data interpretation, and paper revision. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). The APC was funded by Universidade Federal do Pará/Propesp/PROGRAMA DE APOIO À PUBLICAÇÃO QUALIFICADA-PAPQ-EDITAL 02/2023.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committe of Ophir Loyola Hospital, Belém-Pará; protocol code 4,409,317 and date of approval 20 October 2020.

Informed Consent Statement: Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: The results can be found directly in Supplementary Table S1.

Acknowledgments: I would like to thank CAPES , pro-rector of research and postgraduate studies at the Federal University of Pará and postgraduate program in Genetics and Molecular Biology.

Conflicts of Interest: The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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CAPÍTULO 2. UMA ABORDAGEM CITOGENÉTICA, HEMATOLÓGICA E BIOQUÍMICA EM PACIENTES ADULTOS COM LEUCEMIA MIELOIDE AGUDA NA REGIÃO NORTE DO BRASIL.

Em prelo na ACS Bio & Med Chem Au

Cytogenetic Findings and Alterations in Biochemical and Hematological Parameters of Adult Patients with Acute Myeloid Leukemia (AML) from Northern Brazil

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KEYWORDS: Leukemia, AML, Cytogenetics, Hematology, Biochemistry.

ABSTRACT: Acute myeloid leukemia (AML) is a genetically diverse disease with specific somatic mutations. It affects the differentiation of hematopoietic cells, leading to immature cells in peripheral blood. The incidence of AML is 4.2 per 100,000 annually, often with aggressive clinical patterns and an overall survival rate of 25%. Thus, chromosomal changes play a crucial role in cellular transformation, impacting hematopoiesis. The diagnosis involves morphological, immunological and cytogenetic classification, with karyotype analysis as a prognostic marker. In this article, characterized karyotypes in 55 patients with AML from the northern region of Brazil, identifying frequent translocations (e.g., t(9;22), t(6;9), t(8;21), t(9;11)). Notably, 14 patients had normal karyotype. This study also observed that the t(9;22) translocation showed significant differences between the levels of neutrophils, eosinophils, basophils and rods. Biochemical changes were also observed, including changes in glucose and potassium levels. Thus, this study describes cytogenetic changes comparing frequencies with the world population in adult patients with AML in a mixed population from northern Brazil, emphasizing unique proportions and prognostic implications. In addition to showing hematological and biochemical changes associated with t(9;22) translocation and p210/p190 expression and its relationship with prognostic factors in patients with AML.

Introduction

Acute myeloid leukemia (AML) is a heterogeneous genetic disease with specific somatic mutations [1], compromising the differentiation of hematopoietic cells and presenting immature cells in peripherical blood [2]. Per year, the rate of new cases of AML is 4.2 per 100.000, frequently with aggressive clinical patterns and an overall survival rate of 25% [3]. Thus, elderly patients with AML over 65 years of age present ineffective treatment and an adverse prognosis, unlike young and middle-aged patients [4]. In hematological cancers, chromosomal alterations are described as the main initiator of cellular transformation, being related to recurrent genes that regulate hematopoiesis [5,6]. The diagnosis of patients with AML is made through morphological, immunological and cytogenetic classification, with karyotype analysis being an important prognostic reference marker [7,8]. Therefore, cytogenetic abnormalities can provide important information to guide the therapy and prognosis of patients with AML [2,9,10]. Thus, this study aims to characterize, for the first time, cytogenetic alterations and the normal karyotype described in adult patients from the Amazon region with AML. In addition, it evidences associations in hematological and biochemical patterns with cytogenetic and molecular alterations.

Materials and Methods

Ethical Aspects and Patients

This study was approved by the Ethics Committee of Ophir Loyola Hospital, Belém-Pará (number: 4,409,317). The cohort study comprised 56 adult patients of both sexes, represented by 33 men and 23 females, aged over 18 years, diagnosed with acute myeloid leukemia (mean=46.78, SD= 14.75). Patients were from Ophir Loyola Hospital, a reference hospital in the state of Para, Brazil. Additionally, it's important to highlight that the Brazilian Amazon populations have a unique profile, distinct from populations in Africa, Europe, the Americas, and South and East Asia. This uniqueness is due to a high degree of miscegenation [11]. Following this research flowchart [fig1].

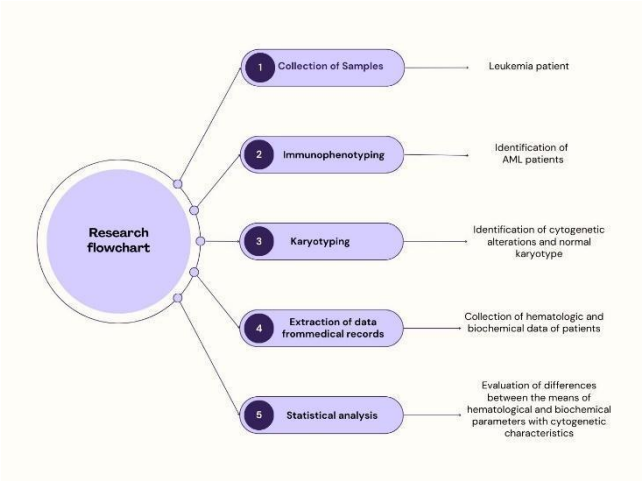


Figure 1. Research and study design stages.

Cytogenetic Characterization

Blood and marrow samples were collected in heparin tubes and transferred to tubes with MarrowMAXTM (Thermo, USA). Samples were collected after 24 h of culture, and 0.1 mL of colchicine was added 2 hours before each collection. They were subsequently centrifuged (1000 rpm for 10 min), the supernatant was removed, and hypotonization treatment started with potassium chloride (KCl) at a concentration of 0.075 M at 37 °C for 20 min. Samples were centrifuged and fixed three times with methanol/acetic acid (3:1). Cell suspensions were placed on histological slides, and then the GTG banding technique was performed [12]. Chromosome classification followed the standards of the International Human Cytogenetic Nomenclature System [13]. Twenty metaphases from each of the patients were analyzed.

BCR::ABL1 transcript: p190 and p210 isoforms

Transcripts of p190 and p210 isoforms were evaluated from patients with AML. The RNA was isolated from bone marrow or peripheral blood using TRI® reagent (Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions. The *BCR::ABL1* transcript was amplified using qRT-PCR One Step/TaqMan PCR Thermo Fisher Scientific, Waltham, MA, USA), which is an assay based on the principle of hydrolysis of oligonucleotides labeled with two fluorophores. Xgen RNA reference kits (IDT, Coral-ville, IA, USA) were used to detect and quantify the p210 and p190 isoforms. The assays were performed in microplates, and for the final quantification of *BCR::ABL* p210 and p190, the transcripts were normalized using the control gene *ABL*. Real-time polymerase chain reactions (qPCR) were conducted on the ABI™ SDS 7300 (Thermo Fisher Scientific, Waltham, MA, USA) under the following conditions: 50 cycles of 10 min at 50°C, 5 min at 95°C, and 1 min at 60°C. The data were corrected following the international standard for linear correlation (R^2): $98 < R^2 < 1000$ and a slope of 3.0 to 3.4. Commercial kits were used qRT-PCR One Step/Taqman, using the principle of oligonucleotide hydrolysis stained with two fluorophores, 20 mL of peripheral blood was collected in a tube containing ethylenediaminetetraacetic acid (EDTA) and treated with a hemolysis buffer. The RNA was stabilized in TRI reagent solution and isolated using 100% isopropanol, chloroform, and 75% ethanol.

Clinical Data and Biochemical and Hematological Exams

In this study, the hematological and biochemical parameters were extracted directly from the medical records of patients with a confirmed diagnosis of AML using immunophenotyping. These parameters, which are evaluated and listed in Table 1, include sex, lineage, occurrence of death, symptoms presented, and clinical risk.

Table 1. Hematological and Biochemical Clinical Parameters.

Hematological Parameters	Biochemical Parameters
Red Cells (million/mm³)	Urea (mg/ dL)
Hemoglobin (g/dL)	Transaminase (AST)/ (U/L)
Hematocrit (%)	Creatine (mg/dL)
Mean corpuscular volume MCV (fL)	Glucose (mg/dL)
Mean Corpuscular Hemoglobin (pg)	Magnesium (mg/dL)
Mean corpuscular hemoglobin concentration (g/dL)	Potassium (mEq/L)
RDW (%)	Sodium (mEq/L)
Leukocytes (mm³)	
Lymphocytes (relative value)/ %	
Lymphocytes (absolute value)/ (mm³)	
Monocyte (relative value)/ %	
Monocyte (absolute value)/ (uL)	
Neutrophil (relative value)/ (%)	
Neutrophil (absolute value)/ (mm³)	
Eosinophil (relative value)/ %	
Eosinophil (absolute value)/ (µL)	
Basophils (relative value)/ %	
Basophils (absolute value)/(uL)	
Rods (relative value)/ (%)	
Rods (absolute value)/(ml/µL)	
Platelets (mm³)	

Statistical Analysis

The calculations and the statistical analysis in this study were performed with R 3.3.0 (R Core Team, 2016). Analyses were performed using Levene's test for distribution analyses and Analysis of Variance (ANOVA). Group data are expressed as mean ± standard deviation (SD). Values of $p \leq 0.05$ were considered significant.

Results

Cytogenetic characterization

This study characterizes the karyotypes of 55 patients diagnosed with Acute Myeloid Leukemia (AML) at Ophir Loyola Hospital (Belém, Pará, Brazil). The most frequently observed translocations among these patients were t(9;22), t(6;9), t(8;21), and t(9;11). Notably, 14 out of the 55 AML patients presented a normal karyotype (Fig.2). Other chromosomal alterations are detailed in Supplementary Table 1.

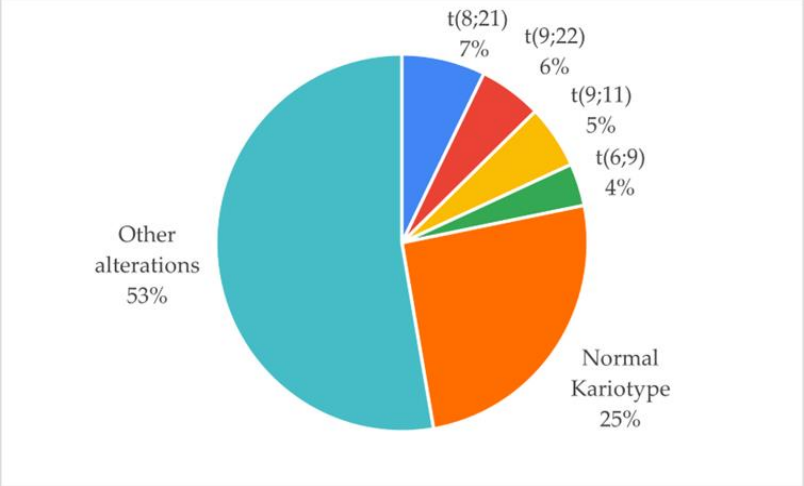


Figure 2.Description of the frequencies of different types of karyotypes observed in 55 patients with AML. Among the translocations, we observed 7% of t(8;21), 6% of t(9;22), 5% of t(9;11), and 4% of t(6;9). In the case of normal karyotypes, we observed a frequency of 25% among the patients. Additionally, 53% had other translocations associated with chromosomal instability described in supplementary table.

Cytogenetic Alterations and Hematological Data

We observed that female patients presented distinct average RDW values compared to men (mean=17.87%, SD=5.112, p=0.01). The t(9:22) showed levels of neutrophils (mean=18939 mm3, SD=31820.6, p=0.01), eosinophils (mean= 1422.9 mm3, SD=34.355, p<0.001), basophils (mean= 1.36 mm3, SD=1.51, p=0.001), and rods cells (mean= 5710.4 ml/µL, SD=9890.7, p=0.001) with significant differences compared to other patients with AML. In this group, specifically, the patients with p210 also demonstrated distinct average values of red blood cells (mean=3.66 m/mm3, SD=0.695) and platelets (mean = 433µl, SD= 211.62) compared to all other patients studied. Meanwhile, patients with p190 expression presented significant differences in the averages of RDW (mean=21.35%, SD=4.909) and platelets (mean = 524.75 µl, SD= 145.43). All results are shown in Table 2.

Table 2. Hematological clinical exam data.

Hematological Parameters		Categories	Mean	Min. Value	Max. Value	SD	*p-Value*
Sex	RDW (%)	Male	14.27	0	24	4.952	0.01
		Female	17.87	12.4	29	5.112	
	Neutrophil (relative value) (%)	Male	20.82	0	64	24.616	0.01
		Female	38.56	0	74	22.252	
t(9;22)	Neutrophil (absolute value) (mm^3)	t(9;22)	18939	0	55676	31820.6	0.003
		Other	28823.89	0	35014	9400.7	
	Eosinophil (relative value) (%)	t(9;22)	20.33	0	60	34.355	0.0002
		Other	1.70	0	16	9.01	
	Eosinophil (absolute value) (mm^3)	t(9;22)	1422.9	0	3198	1627.8	0.001
		Other	68.81	0	835.9	491.136	
	Basophils (relative value) (%)	t(9;22)	1.36	0	3	1.51	0.034
		Other	0.302	0	3	0.851	
	Basophils (absolute value) (mm^3)	t(9;22)	1090.2	0	3212.1	1837.8	0.001
		Other	18.4	0	497.2	461.9	
	Rods (absolute value) (ml/µL)	t(9;22)	5710.4	0	17131	9890.7	0.001
		Other	247.89	0	3230	2498.4	
p210	Red cells (m/mm^3)	p210	3.66	3.11	4.47	0.695	0.04
		Other	2.11	1.95	2.34	0.724	
	Platelet (µl)	p210	433	50	864	211.62	0.005
		Other	100	5	800	179.36	
p190	RDW (%)	p190	21.35	15.3	29.6	4.909	0.025
		Other	15.49	0	24,5	4.95	
	Platelet (µl)	p190	524.75	50	864	145.43	0.001
		Other	76.58	5	324	121.39	

Cytogenetic Alterations and Biochemical Data

Our study also evaluated changes in biochemical parameters in adult patients with ALL. Patients with AML with t(9;22) presented distinct glucose levels compared to other patients, with an average of 167.33 mg/ld (*p*= 0.05, SD= 88.44) [fig 3]. Patients expressing the p210 isoforms showed higher average potassium levels than other patients, with an average of 5.15 mEq/L (*p*= 0.01, SD= 0.52). Similarly, male patients presented higher glucose levels compared to females with AML (mean=127.21 mg/ld, SD= 31.45, *p*= 0.037). All data are available in figure 3 and figure 3.

Table 3. *Biochemical* clinical exam data.

Biochemical Parameters	Categories	Mean	Min. Value	Max. Value	SD	*p-Value*

Sex	Glucose (mg/ld)	Male	127.2174	21	302	31,45	0.037
		Female	94.684	32	152	30,42	
t(9;22)	Glucose (mg/ld)	t(9;22)	167.333	96	300	88.44	0.051
		Other	112.5	21	302	29.71	
P210	Potassium (mEq/L)	t(9;22)	5.15	4.7	5.6	0.52	0.011
		Other	3.84	2	5.6	0.62	

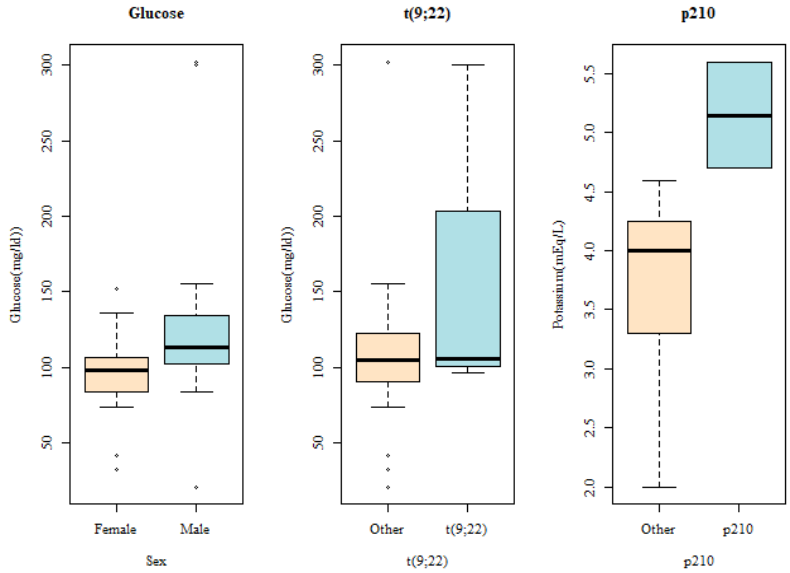


Figure 3.Boxplots showing the distinct glucose values between the sexes of patients with AML (p= 0.037) and t(9;22) (p= 0.05). As well as the potassium values with distinct means in patients with p210 expression (p= 0.01). Through the ANOVA variance analysis test.

Discussion

For the first time, our study characterizes the cytogenetic pattern of patients with adult myeloid leukemia from an admixture population of northern Brazil. It also demonstrates how these karyotype alterations can be associated with changes in hematological and biochemical values, identifying recurring chromosomal rearrangements useful as a tool in managing and accessing risk levels in adult patients with AML, alongside immunophenotyping and molecular diagnosis [10].

Cytogenetic Abnormalities

In our study, t(9;22) translocation is present at a higher frequency (6%) when compared to the global average frequency, which has a mean percentage of 1.8% (SD=0,739) [14-18]. Such translocation forms a *BCR::ABL* fusion oncoprotein [19]. Being classified as a rare and provisional entity for myeloid neoplasia and acute leukemia by the World Health Organization (WHO) [20]. *BCR::ABL* is described as an adverse risk group in the risk classification [21]. Studies suggest combining Tyrosine Kinase Inhibitor (TKI) treatment with allogeneic hematopoietic stem cell transplantation (allo-SCT) due to the poor response to traditional therapy or TKI alone [22]. However, more potent *BCR::ABL* inhibitors, including dasatinib, may be more effective than previous inhibitors. They are effective in elderly

patients with low tumor burden and without chromosomal abnormalities or mutations in the ABL kinase domain that confer resistance to TKI treatment [23].

We observed that 5% of AML patients had the t(9;11) translocation. Worldwide, the t(9;11) frequency associated with the *KMT2A::MLLT3* gene is 1.1% (SD=0,51) [24-26]. Such translocation normally forms 11q23/KMT2A rearrangement (lysine methyltransferase 2a gene), generating a fusion of *KMT2A* with the *MLLT3* gene; such translocation is recognized as a disease specific entity for myeloid neoplasia and acute leukemia [27]. In addition, the prognosis of patients with such a translocation depends on their age; younger patients have a favorable prognosis, while older patients have an unfavorable prognosis [27,28]. After treatment with topoisomerase II inhibitors, there is an increase in the frequency of 11q23/KMT2A rearrangement, presenting an unfavorable therapeutic clinical outcome in patients with AML [28,29].

The chromosomal translocation t(8;21) was observed in 7% of the patients in this study, a value exceeding the global average of 5% (SD=1,66%) [15,25,30-34]. The t(8;21)(q22;q22.1) translocation results in a new chimeric gene, *RUNX1-RUNX1T1*, which is derived from chromosome 8 [35]. This fusion directly regulates transcription and inhibits differentiation, thereby contributing to the progression of leukemia in cooperation with the MGA gene (Max-gene associated) [36]. Such fusion is associated with a good prognosis in patients with AML [37]. In the presence of this type of fusion, the chemotherapy approach continues to be the basis of treatment; in the induction and remission phases, high doses of nucleoside analogs (for example, cytarabine) are administered, combined with anthracyclines (idarubicin or daunorubicin) [38,39].

We found that 4% of cytogenetic changes are relative to the presence of a translocation t(6;9). We noticed that this frequency is high compared to the global frequency of t(6;9), which is 3.5% [40-45]. This structural chromosomal translocation encodes a *DEK-CAN* fusion protein, transforming immature hematopoietic stem and progenitor cells (HSPCs) in which the *FLT3* promoter is not active [46]. According to the WHO, due to its biological and clinical characteristics, the t(6;9) translocation is classified as a distinct entity [47]. As also observed in this study, the majority of patients with AML and t(6;9) translocation are young, between 22 and 40 years old [48,49]. Patients have a median survival after diagnosis of around 1 year, and complete remission (CR) rates do not exceed 50% since t(6;9) remains an independent adverse risk characteristic [50,51]. Thus, hematopoietic stem cell transplantation (HSCT) is the recommended current curative approach for patients with AML and t(6;9)[52].

In our research, we noticed that 25% of the patients we examined had a normal karyotype. In these cases, molecular biology is extremely important in the search for biomarkers, since the onset, progression and prognosis of AML are related to genetic mutations [53]. Molecular studies describe those mutations in *NPM1*, *CEBPA* and *GATA2* are related to a favorable prognosis [54,55], while mutations in *FLT3-ITD*, *RUNX1*, *ASXL1*, *MLL*, *TP53*, *PHF6* and *U2AF1* are associated with an adverse prognosis in patients with AML [56,57].

Hematological Modifications

Our study observed that patients with AML and t(9;22) showed average values of eosinophils (mean=1422.9/mm3, SD=34.355, p<0.001), basophils (mean=1.36/mm3, SD=1.51, p=0.001), and rods (mean=5710.4, SD=9890.7, p=0.001) were elevated and significantly different compared to other AML patients. Nonetheless, neutrophil counts (mean=18939/mm3, SD=31820.6, p=0.01) were lower in comparison with other patients. Hematopoietic models indicate that the expression of p210 *BCR::ABL* fusion exclusively allows myeloid lineage commitment and differentiation from hematopoietic stem cells (HSCs), compromising lymphoid lineage commitment of HSCs through the suppression of B cell signal transduction [58], it may explain the hematological parameter differences found in patients with t(9;22). The values of basophils, eosinophils and neutrophils are above the normal reference ranges in laboratory parameters in patients with t(9;22) [59,60]. The presence of basophilia is an independent prognostic indicator in Chronic Myeloid Leukemia (CML) Ph+, and there is an increase in basophil levels as the disease progresses, which is a criterion included in most prognostic classification systems for CML [61,62]. The prognostic importance of basophilia has been validated in patients treated with imatinib or other *BCR::ABL1* inhibitors, one of the most significant and well established risk factors in CML [63,64]. The increase in basophils and eosinophils in patients with AML is often an intriguing diagnostic situation that necessitates special investigation due to its clinical relevance [65]. Therefore, we can suggest that the basophilia found may also be a prognostic and diagnostic parameter in AML patients with t(9;22).

In our study, patients who expressed p210 and p190 exhibited elevated platelet levels with distinct averages among the patients (p=0.001 and p=0.005, respectively). This increase in platelet count was associated with the presence of specific types of *BCR::ABL1* mRNA variants in patients with CML, suggesting that this parameter could be a potential indicator of translocation [66,67]. In patients with AML, platelets can be used to predict long-term and independent

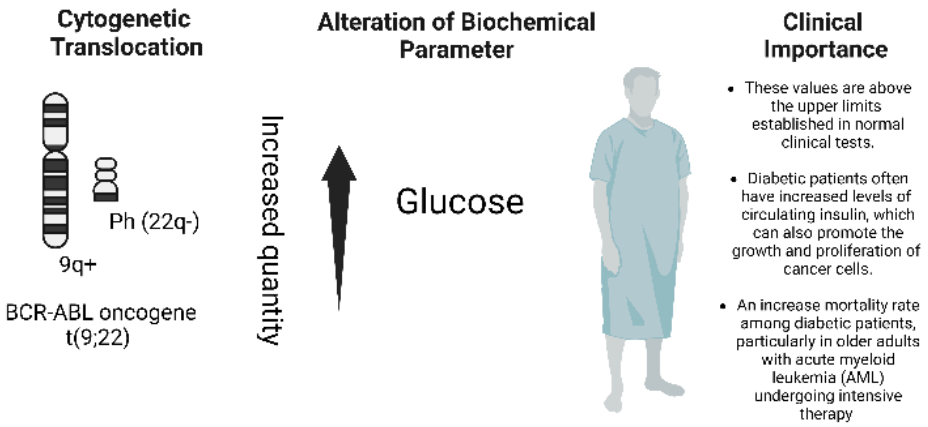
prognosis; in this context, a poor prognosis has been associated with a low platelet-to-lymphocyte ratio, mean platelet volume, and high platelet distribution width [68].

These patients with p210 expression showed higher mean red cell values compared to other patients (p=0.04). This is an important clinical parameter, as a low ratio between hemoglobin and red cell distribution width (RDW) is associated with shorter overall survival and disease progression in cancer patients, making it a potential clinical biomarker [69]. Patients with p190 expression had higher mean levels of red cell distribution width (RDW) compared to other patients (p=0.025). These mean values exceeded what is considered normal in healthy individuals [59]. Studies have demonstrated a correlation between RDW and survival outcomes in patients with hematological malignancies, where higher RDW levels are associated with a worse prognosis than those with lower RDW [70]. In this context, elevated cytokine levels may alter iron metabolism, leading to increased hepcidin levels and oxidative stress. Simultaneously, erythropoietin production is reduced, resulting in higher RDW values [71]. Additionally, Ph+ ALL patients with p190 and p210 variants may exhibit hematological changes, distinct clinical features, varied outcomes, *ABL1* mutation profiles, and different transcriptomic characteristics. Notably, allogeneic hematopoietic stem cell transplantation (Allo-HSCT) could potentially enhance outcomes in patients with p210 [72].

Biochemical Alterations

Regarding patients with p210 expression these presented mean potassium values with significant differences compared to the other patients (p=0.011). These averages are above the reference values of biochemical markers for healthy people [73]. Such high values may be related to the positive regulation of the voltage-dependent potassium channel hEag1 in patients. In AML, it is highly expressed in the most common subtypes and correlates with increasing age, higher relapse rates and significantly lower overall survival, being an independent predictive factor for poor outcomes. [74]. The evaluation of the biochemical profile takes place due to the importance of nutritional, medical, and monitoring in order to improve the quality of life and tolerance of patients to treatment [75].

We found that glucose levels in patients with t(9;22) and male patients had higher averages compared to other patients (p=0.05, p=0.037, respectively). These values are above the upper limits established in normal clinical tests [73]. The elevation of circulating glucose levels provides malignant cells with greater access to glucose, thus creating a conducive environment that supplies the necessary nutrients for cancer development and growth. Diabetic patients often have increased levels of circulating insulin, which can also promote the growth and proliferation of cancer cells [76]. Similarly, a retrospective study revealed an increase in the 30-day mortality rate among diabetic patients, particularly in older adults with acute myeloid leukemia (AML) undergoing intensive therapy. However, in the case-control study, no associations were found between leukemia, diabetes, survival, and glycemic control [77]. As described in scheme 1.



Scheme 1. t(9;22) and elevated glucose levels in AML patients.

Conclusions

This is one of the first studies to describe the frequency of cytogenetic translocations in patients with acute myeloid leukemia (AML) within an admixed population from northern Brazil. It highlights distinct proportions compared to

other regions and emphasizes their prognostic impact. Additionally, we present hematological and biochemical alterations associated with the t(9;22) translocation, underscoring its significance as a prognostic and translocation indicator in AML patients. We emphasize the need for future studies with larger patient cohorts to validate our findings and contribute to improved treatment strategies for AML.

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Author Contributions

Dejair S. Duarte, Rommel R. Burbano, and André S. Khayat. conceptualized the study and designed the research. Dejair S. Duarte, Eliel B. Teixeira, André S. Khayat, and Rommel R. Burbano. performed the research. Thiago X. Carneiro, Lucyana B. C. Leão, Fernando A. R. M. Júnior, Debora M. Carneiro, and Patricia F. Nunes analyzed the data. Dejair S. Duarte, Eliel B. Teixeira, Marcelo B. Oliveira, and André S. Khayat wrote the paper. Diego D. F. Á. Alcantara, Amanda N. Cohen-Paes, Rommel R. Burbano, Eliel B. Teixeira, Marcelo B. Oliveira, Fernando A. R. M. Júnior, Dejair S. Duarte, and Amanda N. Cohen-Paes contributed to scientific discussion, data interpretation, and paper revision. All authors have read and agreed to the published version of the manuscript.

Funding Sources

This research was funded by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). Through the Consortium of CAPES and ACS journal under a CC BY open access license with your institution's support.

ACKNOWLEDGMENT

I would like to thank CAPES, PROPESP at the Federal University of Pará and Postgraduate Pro-gram in Genetics and Molecular Biology for the opportunity. My parents, wife Aliceane Aguiar, daughter Selena Marie and my doctoral advisors, Professor Dr. Rommel Burbano and Professor Dr. André Khayat. As well as my friend Susanne Santos for helping us with the construction of the graphs and my friend Jhony with the schemes.

ABBREVIATIONS

AML, acute myeloid leukemia; SD, standard deviation; KCl, potassium chloride; PCR, polymerase chain reactions; EDTA, ethylenediaminetetraacetic acid; ANOVA, Analysis of Variance; RDW, Red Cell Distribution Width; WHO, World Health Organization; allo-SCT, allogeneic hematopoietic stem cell transplantation; TKI, tyrosine kinase inhibitor; HSPCs, immature hematopoietic stem and progenitor cells; CML, chronic myeloid leukemia; Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

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Chromosomal Instability in Adult Patients with Acute Leukemias in a Mixed Population from Northern Brazil

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Abstract: Acute leukemia (AL) is a form of blood cancer that begins in the bone marrow. Therefore, the attributes of chromosomal instability (CIN) can enhance risk stratifications and create new opportunities for therapeutic approaches in cancer treatment. Consequently, this study seeks to characterize CIN and ploidy in adult patients with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) in a diverse population, as well as to assess their prognostic implications. **Methods**: This study, approved by the Ethics Committee of Ophir Loyola Hospital, involved 56 adult AML patients and 50 ALL patients. Blood and marrow samples were collected, cultured, and treated with potassium chloride and colchicine, followed by GTG banding for chromosomal analysis. Chromosome classification adhered to the International Human Cytogenetic Nomenclature System, with 20 metaphases analyzed per patient. **Results:** Our study highlights the impact of chromosomal instability in adult acute leukemia patients from Northern Brazil, identifying high frequencies of trisomy 21 and 8 in ALL patients with significant cytogenetic associations. Specific deletions like del(6q) and del(9p) were linked to poor outcomes in ALL patients. For AML patients, 36% exhibited CIN with 16% having cytogenetic translocations, emphasizing the prognostic importance of trisomy 8 and monosomy 7. **Conclusions**: These alterations are crucial for risk stratification and treatment planning, emphasizing the need for tailored therapeutic approaches in adults patients.

Citation: To be added by editorial staff during production.

Academic Editor: Firstname Lastname

Received: date
Revised: date
Accepted: date
Published: date

Keywords: Acute Leukemias; Chromosomal Instability; Adult Patients

Acute leukemia (AL) is a type of blood cancer that originates in the bone marrow (BM) [1]. In the case of acute lymphoblastic leukemia (ALL), this disease develops from precursor lymphoid cells of B and T cells, with B-ALL representing about 75% of all ALL cases. Adult patients with ALL are more challenging to treat and have a worse prognosis [2]. Acute myeloid leukemia (AML) arises due to the accumulation of abnormal blasts in the bone marrow, leading to bone marrow failure, which is the most common underlying cause of death. Among the cytogenetic alterations, chromosomal instability (CIN) is a distinctive feature of cancer, representing the increasing rate at which cells acquire new chromosomal alterations. CIN can be classified into numerical CIN (nCIN) and structural CIN (sCIN) [3]. Thus, the characteristics of chromosomal instability (CIN) not only can refine risk stratifications but also offer opportunities for new therapeutic approaches in cancer treatment [4-6]. Despite CIN being widely present in various aneuploid cancers and having clinical importance, its occurrence in adult acute leukemias has not been sufficiently described, especially in a mixed population. Therefore, this study aims to describe CIN and ploidy in adult patients with ALL and AML in a mixed population and their prognostic impacts.

2. Materials and Methods

2.1. Ethical Aspects and Patients

This study was approved by the Ethics Committee of Ophir Loyola Hospital, Belém-Pará (number: 4,409,317). The cohort study comprised 56 adult patients of both sexes, represented by 33 men and 23 females, aged over 18 years, diagnosed with acute myeloid leukemia (mean=46.78, SD= 14.75) and 50 adult patients of both sexes, with acute limphoblastic leukemia. Patients were from Ophir Loyola Hospital, a reference hospital in the state of Para, Brazil. Additionally, it's important to highlight that the Brazilian Amazon populations have a unique profile, distinct from populations in Africa, Europe, the Americas, and South and East Asia. This uniqueness is due to a high degree of miscegenation [7].

2.2. Cytogenetic Characterization

Blood and marrow samples were collected in heparin tubes and transferred to tubes with MarrowMAXTM (Thermo, USA). Samples were collected after 24 h of culture, and 0.1 mL of colchicine was added 2 hours before each collection. They were subsequently centrifuged (1000 rpm for 10 min), the supernatant was removed, and hypotonization treatment started with potassium chloride (KCl) at a concentration of 0.075 M at 37 °C for 20 min. Samples were centrifuged and fixed three times with methanol/acetic acid (3:1). Cell suspensions were placed on histological slides, and then the GTG banding technique was performed [8]. Chromosome classification followed the standards of the International Human Cytogenetic Nomenclature System [9]. Twenty metaphases from each of the patients were analyzed.

2.3. Immunophenotyping

As amostras de sangue foram coletadas e para preencher cada tubo já identificado, com 100 microlitros de sangue periférico total, ou medula

óssea com ou sem diluição. Na penumbra ou escuro, o que for possível, acrescentar 7 microlitros de cada monoclonal especificado em cada tubo identificado, homogeneizar o anticorpo com a amostra. Desprezar a ponteira a cada homogeneização. Depois foi incubado 10 minutos na penumbra ou escuro. Ocorreu o preenchimento de cada tubo com 1 ml da solução de lise excellise diluída. Foi homogeneizado cada tubo em vórtex e incubado por 10 a 15 minutos no escuro. É adicionado 2ml de PBS e Vortexar e centrifugado por 3 min a 3000 RPM (Rotação Por Minuto). Remover o sobrenadante, e preencher cada tubo com 1ml de PBS. Homogeneizar cada tubo em vórtex, para o processamento da técnica de permeabilização,preencher cada tubo com 100 microlitro da amostra do paciente e 100 microlitro do fixador e da solução de permeabilização, homogeneizar esta solução desprezar a ponteira. Incubar os tubos por 15 minutos no escuro. Preencher cada tubo com 2ml de solução de PBS de uso. Centrifugar todas as amostras por 3 minutos a 6.000 rpm. Desprezar o sobrenadante e acrescentar em cada tubo 100 microlitro da solução B de permeabilização mais 6 l de anticorpo conforme identificado no tubo. Homogeneizar cada tubo em vórtex e incubá-los por 15 minutos no escuro. Preencher cada tubo com 2ml de solução de PBS de uso. Centrifugar todas as amostras por 3 minutos a 6.000 rpm. Desprezar o sobrenadante e preencher cada tubo com 1ml de solução de PBS de uso, e homogeneizar cada tubo em vórtex. Being analyzed by flow cytometry by Attune Flow Cytometers, Thermo Fisher Scientific. Using the international protocol for multiparameter flow cytometry in the diagnosis and management of Acute Leukemia [10].

3. Results

3.1. Acute Lymphoblastic Leukemia

Our studies described 105 karyotypes of adult patients with acute leukemias in the northern region of Brazil. Of these, 50 patients had acute lymphoblastic leukemias [tab1], with 36% presenting chromosomal instability with translocations, 28% with chromosomal instability, 24% with cytogenetic translocation, and 12% with a normal karyotype [fig.1]

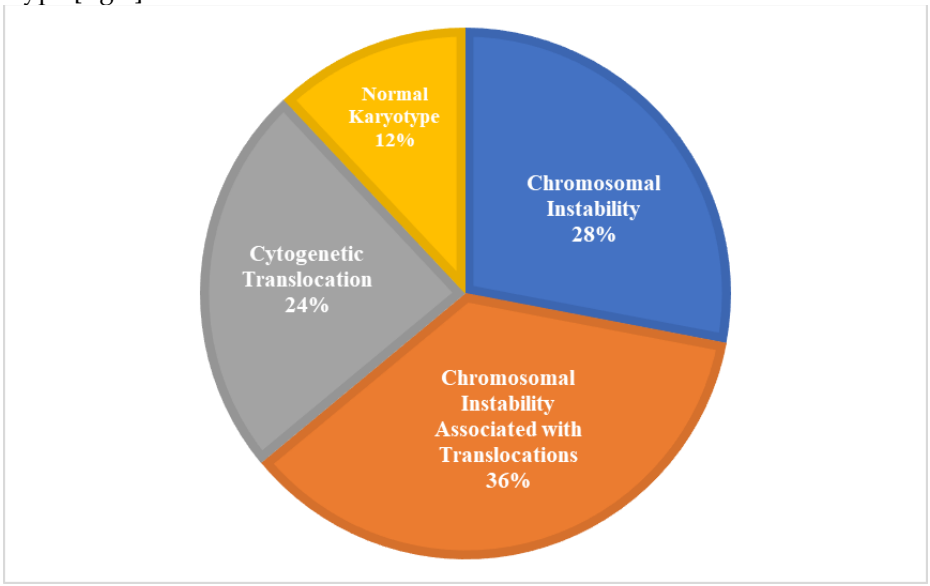

Figure 1. Proportion of cytogenetic profile found in 50 karyotypes of adult patients with ALL.

Regarding numerical chromosomal alterations and translocations, we observed a higher frequency of trisomy 21 in 17/50 in patients, mainly associated with the t(9;22) and t(1;19) translocations, with one case associated with t(1;7) and another with t(10;14). We also observed cases of trisomy 8 in 6% of the patients associated with t(4;11), t(1;19), and t(10;14). Additionally, we identified monosomies of chromosomes 7 and 13 in 3/50 patients in our study. Concerning chromosomal deletions, we observed a higher frequency of del(6q) and del(9p) in patients with chromosomal instability, associated with cytogenetic translocations such as t(1;19) and t(9;22) [table 1].

3.2 Hypodiploidy e Hyperdiploidy in patients ALL.

Our study observed a higher frequency of low hyperdiploidy (aneuploidy between 47-50 chromosomes) among the patients evaluated and a lower frequency of high hypodiploidy (aneuploidy between 40–44 chromosomes), as well as the presence of isochromosomes and deletions associated with translocation [tab 1].

	Karyotypes
Low Hyperdiploidy (Aneuploidy 47–50 chromosomes)	47, XX,t(4;11) + 8
	48, XX,+16, +21
	47, XX +21
	47, XY,t(9;22),+21.
	47, XY, t(9;22), +21
	47, XY, t (9;22), +21
	48, XY, t(9;22),+der(22),+21
	47, XX, der(7)t(1;7), t(9;22), +21
	50,XX, +4, t(9;22), t(12;21), +14, +18, +21
	48,XY, t(1;19), +8, +21
	47,XX,t(1;19),i(17q),+21
	47, XY, t(1;19), del(6q) +21
	47, XX, +5, del(6q)
	49, XY,+4, del(6q), +6, +10, del(12p), -13, +18
	49, XY, +3, +8, t(10;14)(q24;q11), -12, +14, -17,+21,+22
	47, XX, i(9q), +21
	48, XX, trp(1q), t(3;12), -7, +13, +13
	47,XY,t(12;21), +21
	47 XY, t(10;14), +20
	47, XX, del(1q), +der(7)t(7;19), -19, +21
Hipoploidia (40–44 chromosomes)	44, XX,del(6q), del(12q), -13, -17
	42, XX, -X, -6, del(12p), -13, -17
Deletions	46, XY, t(1;19), del(9p)
	46, XX, -7, del(9p), +21
	46, XY, del(9p)
	46, XY, del(9p), del(13q), +21
	46, XX, del(6q), t(9;22)
	46, XX, del(6q).
	46, XY, del(5q), del(6q)e del(12p).

Table 1. Karyotypes found in 50 adult ALL patients from Ophir Loyola Hospital distributed according to the WHO ALL classification.

3.3 Acute Myeloid Leukemia

In our evaluation of adult patients with acute myeloid leukemia, we described 55 karyotypes as detailed in Table 2. Among the patients, 36% exhibited chromosomal instability, 15% showed chromosomal instability associated with translocations, 24% had cytogenetic translocations only, and 25% had a normal karyotype [Figure 2].

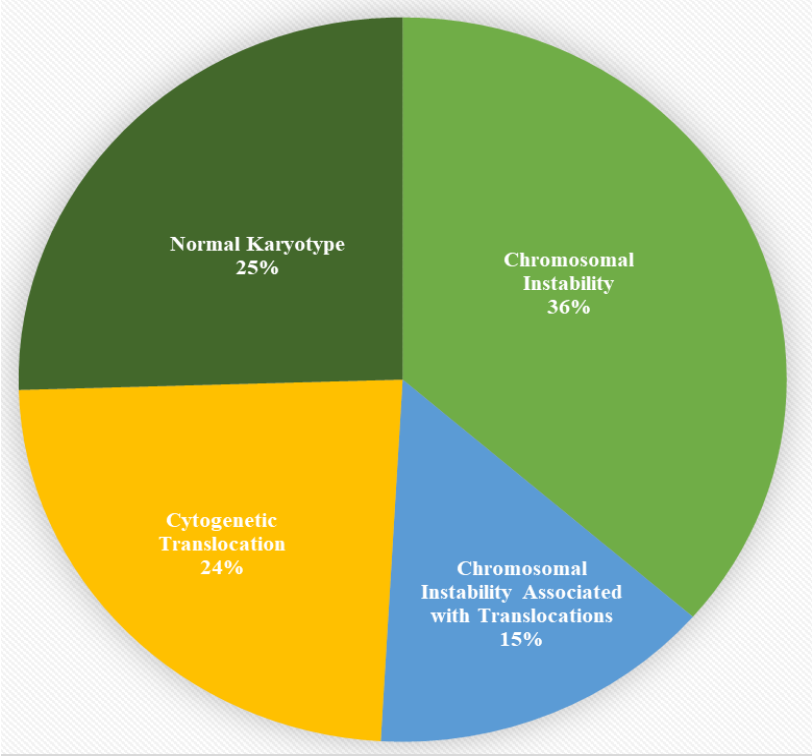

Figure 2. Proportion of cytogenetic profile found in 55 karyotypes of adult patients with AML.

Concerning chromosomal gains and losses in the karyotypes of the studied AML patients, we observed a high frequency of aneuploidies involving chromosome 8 (6/55 patients), with lower frequencies of aneuploidies in chromosomes 12 and 21. Additionally, the loss of chromosome 7 was frequently observed among the studied patients (4/55)[Table 2]

In terms of cytogenetic subtypes, low hyperdiploidy (aneuploidies with 47-50 chromosomes) was the most frequent, observed in approximately 29% of cases. High hypodiploidy (aneuploidy with 40–45 chromosomes) had a frequency of 16%, while other alterations were found in 12% of cases, as shown in Table 2.

Subtype	Karyotypes
Hyperdiploidy	48,XY,+9,+21,/46,XY
	48,XY,+8, t(9;22), +12
	47,XX,t(9;22),+19
	47, XX,t(9;11) +6
	47, XX, inv (16), +8
	47, XX, dup(1q), +8
	47,XY,+8,t(15;17)
	47,XX, del(5q). +8
	47,XX,+8
	47,XY,+8{14}/46,XY{6}
	47,XY,+21
Hypodiploidy	45,XX,-7
	45,XX,-7
	45, XX, t(8;21)(q22;q22), -7
	45, X, -Y, t(8;21)
	45,X, -Y,del(7) (q11.2), t(8;2) (q22;q22), -9
	45,XX,t(3;3),t(5;12),-7
	45, X, -Y, dup(11q)
	45,XX,inv(3q),i(7),-17
	45,XY,-5,del(12P)
	43-44,XY,-5,DEL(6) (q15q21),-8,INV(12) (p12p13), -15,ADD(15) (p11.2), -17, DER(19) t(19;?) (p13;?), -21,-22
	43, -X, Y, -7, -21
Deletions	46,XX,del(7q)
	46,XY,del(7)(q22q34)
Others	46,XX,t(3;21),-7,+12
	46, XY, inv(16)(p13q22)
	46,XY, inv(3q), t(7;11), t(12;13)
	46,XY,t(4;11),i(7q)
	46,X,der(X) t(x,?) (q24;?), del(5) (q31q35), t(8;21) (q22;q22)

Table 2. Numerical and structural cytogenetic alterations among patients with AML, classified according to the ICC classification and the 5th WHO classification of AML.

4. Discussion

Our study is one of the first to describe chromosomal instability in adult patients with acute leukemias in a mixed population from Northern Brazil, highlighting the prognostic impact of such cytogenetic alterations in patients with AML and ALL.

4.1 Chromosomal Instability in Patients with ALL

In our study, we noted that 36% of patients exhibited chromosomal instability associated with translocations, and 28% had chromosomal instability alone. This information is significant because CIN has been associated with tumorigenesis, therapeutic resistance, and poor survival outcomes in numerous types of human cancers (11-14). Such characteristics are observed in PDX models of cB-ALL, where variable levels of ongoing CIN are significantly associated with leukemia progression in mice [15].

Thus, strategies to modulate CIN levels in cancer cells are explored therapeutically [14]. The increase in CIN levels in tumors undergoing CIN has been explored as a strategy to push them beyond their tolerance threshold, potentially enhancing the efficacy of certain cancer treatments, such as paclitaxel and radiation therapy [16-17]. Conversely, reducing CIN levels by manipulating key mitotic pathways, such as the spindle-assembly checkpoint (SAC) and microtubule dynamics, has resulted in a significant improvement in overall survival (OS) in preclinical mouse models [18-19]. Clinical outcomes have been shown to depend on the specific aneuploidies produced by CIN, as relative cellular fitness is influenced by the expression of genes located on the affected chromosomes [20-23].

4.2 Numerical chromosomal alterations and translocations in ALL

We observed a high frequency of trisomy 21 in the evaluated adult ALL patients, approximately 30%. This duplication is present in 78% of relapsed patient cases and also in 15% of patients at initial diagnosis, resulting in an extra RUNX1 allele in cases of trisomy 21 [24], and is associated with poorer outcomes, especially in relapsed patients [25]. Gains of one or more copies of the entire chromosome 21 are extremely common in this type of cancer, being the only chromosome consistently overrepresented in high hyperdiploid, hypodiploid, and near-haploid ALL [26-27]. However, we observed a significant association with t(9;22) and t(1;19). Acquired trisomy 21 is associated with poor prognosis in BCR::ABL+ leukemias and may be related to imatinib resistance in Ph+ ALL patients [28]. In the case of t(1;19) associated with the gain of chromosome 21, no studies have shown the prognostic impact in adult ALL patients. However, in contrast to pediatric ALL-B with t(1;19), adult patients exhibit poor outcomes with intensive chemotherapy regimens. Although an initially favorable response to MRD-targeted therapy is observed, relapses are common, leading to poor long-term outcomes [29]. There is also a case report of an adult patient with Down syndrome and ALL with t(1;19)(q23;p13)/TCF3-PBX1, who experienced an unfavorable outcome during treatment [30].

In our study, we observed a 6% frequency of chromosome 8 trisomy. Studies indicate a frequency of 10% and an unfavorable prognosis in patients with ALL [31]. However, trisomy 8 can rarely occur in acute lymphoblastic leukemia [32-33], as we observed in our study population. In myeloid malignancies, monosomy 7 is the most common chromosomal abnormality and is associated with a poor prognosis, with an overall survival rate of 0-3% [34]. Monosomy 7 is also

found in approximately 10% of precursor B-cell ALL cases, being particularly common in near-haploid, low-hypodiploid, and BCR-ABL positive cases, but not as a sole monosomy 7 abnormality [35]. However, our study showed a lower frequency in our cohort, with monosomy 7 present in only one patient with the t(9;22) translocation. Similarly, the case of granular acute lymphoblastic leukemia in an adult with poor clinical outcome may be associated with the DNMT3A variant combined with monosomy 7 [36].

del(6q)

Deletion of the del(6q) was the most common deletion among patients with chromosomal instability, present in 7/50 patients evaluated. A high incidence of 6q deletions (20%) was observed in a review including 164 cases of *ETV6::RUNX1*-ALL [37]. In B-ALL, 6q deletions involving *FOXO3* and/or *PRDM1* may promote leukemia survival, partly by reducing sensitivity to leptin receptor signaling [38]. *PRDM1* holds a crucial role in regulating human T cell memory by driving T cell exhaustion. The combined disruption of PRDM1 and NR4A3 expression or function has the potential to generate genetically reprogrammed T cells, enhancing both immediate and long-term antitumor responses [39]. The loss of *PRDM1*/*BLIMP-1* function contributes to the poor overall prognosis of activated B-cell-like (ABC) diffuse large B-cell lymphoma (DLBCL) patients [40]. It is important to recognize that the loss of *POU3F2*, *PRDM13*, *SIM1*, and *FAXC* may also contribute to the leukemogenic potential of large 6q deletions, as well as *CCNC* and *BACH2*, which are implicated in other B-ALL subtypes, although their function in B cells is currently unknown [41-42].

del(9p)

The del(9p) was identified in 4 out of 50 patients, approximately 8% of the study cohort. Studies show that deletions of 6q and 9p (including the *CDKN2A* gene), numerous trisomies (chromosomes 21, 4, 10, 16), and an extra copy of *RUNX1* are associated with poorer outcomes, especially in relapsed patients [43-45]. The 9p deletion is associated with the loss of the *MTAP, CDKN2A, CDKN2B, DMRTA1*, and *FLJ35282* genes [46]. Deletions are the most prevalent alterations in the *CDKN2A* gene, found in approximately 25% of patients with ALL, including 5-20% of those with B-cell precursors [47]. Alongside PAX5 deletion due to loss by deletion in the 9p chromosomal region in pediatric patients [48]. The presence of *CDKN2A*/*2B* deletion is associated with adverse overall survival and event-free survival outcomes in pediatric and adult patients with ALL [49].

4.4 Characteristics of B-ALL subtypes.

Our study showed that most evaluated patients with CIN had a karyotype with low hyperdiploidy (aneuploidy 47-50 chromosomes), with a frequency of 29%, higher than reported in the literature. Hyperdiploidy is divided into two subcategories: high hyperdiploidy (51-65 chromosomes), with a frequency of 10% in adults with ALL (Inaba et al., 2020), and low hyperdiploidy (47-50 chromosomes), with a frequency of 10-15% in adult patients, increasing with age [50]. However, low hyperdiploidy is associated with a poor prognosis and shorter survival periods compared to high hyperdiploidy [51].

In our study cohort, 16% of the patients were cytogenetically classified as hypodiploid, with most cases being near-diploid and two cases classified as high hypodiploid among the 50 evaluated patients. This is a higher frequency compared to the literature. The current classification for B-ALL with hypodiploidy is formally divided into two categories: B-ALL, low hypodiploid (32-39 chromosomes) and B-ALL,

near-haploid (24-31 chromosomes) [52]. However, hypodiploid karyotype occurs in less than 7% of children and adults with B-ALL. Most hypodiploid cases present with 45 chromosomes and are classified as near-diploid ALL, which does not have as poor a clinical outcome as typical hypodiploidy. These cases also present with lower leukocyte counts at diagnosis compared to other B-ALL patients without hypodiploidy [26,53]. Nevertheless, hematopoietic stem cell transplantation does not improve the poor outcomes of children with hypodiploid acute lymphoblastic leukemia [54]. Currently, for treating B-ALL hypodiploid patients with fewer than 40 chromosomes, immunotherapeutic approaches are being used, such as monoclonal antibodies, chimeric antigen receptor (CAR) T cells, and bispecific T-cell engagers (BiTEs), including inotuzumab and blinatumomab [55].

4.5 Chromosomal Instability in Adults Patients with AML

Among the 55 patients evaluated in this study, 36% presented chromosomal instability (CIN) and 16% had cytogenetic translocations. Certain features of CIN can refine risk stratifications and create opportunities for new therapeutic approaches in cancer [56-57]. In the case of AML, a heterogeneous disease characterized by the abnormal proliferation and accumulation of myeloid precursor cells in the bone marrow, CIN and its signatures are widely found [58]. These cytogenetic alterations are a crucial prognostic factor in AML, used for risk stratification and treatment definition, with about 55% of AML patients having chromosomal abnormalities, regardless of classification [33,50].

4.6 Numerical chromosomal alterations and translocations in AML

We observed a high frequency of aneuploidies involving chromosome 8 (6/55 patients) at 10.9% in adult AML patients. Trisomy 8 is one of the most common numerical aberrations in AML, occurring with a frequency of 10-15% [59-60]. This unique cytogenetic alteration is present in 30-40% of cases and occurs together with other cytogenetic aberrations in 60-70% of cases, in both adult and pediatric AML [61-64]. Regarding mutations, *RUNX1* frequently occurs in AML with trisomy 8, approximately 25-35% [65-67]. In AML with trisomy 8, mutations in chromatin modifiers such as *ASXL1* occur in 20-50% of patients with a sole trisomy 8 [68-69]. In this case, the *ASXL1* mutation and the *RUNX1* mutation appear to frequently cooperate, playing an important role in leukemogenesis [59;70], and there may be a possibility of co-occurrence of these two mutations in patients with AML with trisomy 8 [71]. Patients with AML and trisomy 8 as the sole abnormality are classified as intermediate risk and should be considered for allo-HSCT, as the co-occurrence of high-risk mutations such as *FLT3-ITD*, *RUNX1*, *ASXL1* and *TP53* clearly strengthens the indication for allo-HSCT as the preferred consolidation therapy [33,72]. Other approaches needed for patients without a suitable donor include repeated cycles of high/intermediate-dose cytarabine or autologous hematopoietic stem cell transplantation (auto-HSCT) [73].

Monosomy 7 was observed in 7% of patients (5/55). Similar frequencies were observed in 7% of primary acute myeloid leukemia (pAML) and 12% of secondary MDS/AML (MDS/sAML) and are associated with a poor prognosis, with no prognostic difference between del7q/-7 in myeloid neoplasms [74]. Recent studies suggest that chr. 7 aberrations may be secondary to molecular lesions [75]. Studies show that the haploinsufficient (HI) genes that most faithfully phenocopy the

pro-leukemogenic effects involved in the deletion are *CUL1*, *CUX1*, *EZH2*, *KMT2C*, *LUC7L2*, *SAMD9*, as well as several bona fide TSGs (*KRIT1*, *RINT1*, *XRCC2*, *NRF1*) and a variety of other potential TSGs involved in DNA damage response, DNA replication, and chromatin regulation [74,34,76].

4.7 Hyperploidies and Hypoploidies in AML Patients

We observed that within the study cohort, most cases with hyperploidy without structural alterations were associated with the gain of chromosome 8, approximately 0.09%. The same proportion was found in patients with hyperploidy and structural alterations. This information is important because patients with only numerical cytogenetic alterations and no structural abnormalities have better survival rates compared to patients with three or more cytogenetic alterations with structural abnormalities [77]. However, we found a frequency of 16% of adult AML patients with monosomies, mainly involving the loss of chromosome 7 [tab4]. In general, the monosomic karyotype shows a particularly poor prognosis, even after allogeneic hematopoietic stem cell transplantation [78,79]. It is worth noting that we did not observe complex karyotypes (≥ three unrelated chromosomal abnormalities in the absence of other defined class recurrent genetic abnormalities) in this study group. According to the ICC and ELN 2022, risk stratification classification follows a hierarchy: AML with *TP53* mutation takes precedence over AML with myelodysplasia-related genetic mutations, which in turn takes precedence over AML with myelodysplasia-related cytogenetic abnormalities [80].

4.8 Clinical Trials in Patients with Acute Leukemias

In the case of patients with ALL and chromosomal instabilities who frequently present refractoriness and relapse during treatment, in these cases, a new treatment program with Venetoclax and Navitoclax has been approved (Clinical Trials: NCT05215405).

Regarding patients with AML and chromosomal instabilities associated with trisomy 8, two new therapies have been approved for patients with important IDH1 and FLT3 mutations with Ivosedenib and Gilteritinib (Clinical Trials: NCT03245424 and NCT03070093), respectively. It is important to note that these are mutations that can help predict the prognosis for patients and may be useful in their treatment.

5. Conclusions

In conclusion, our study provides valuable insights into chromosomal instability in adult patients with acute leukemias from a mixed population in Northern Brazil. We also identified high frequencies of trisomy 21 and chromosome 8 trisomy in ALL patients, along with significant associations with cytogenetic abnormalities such as t(9;22) and t(1;19). Our study further highlighted the prevalence of specific deletions, such as del(6q) and del(9p), which are linked to poor outcomes and therapeutic challenges in ALL patients. Importantly, our findings indicate that patients with hyperdiploidy and hypodiploidy present distinct prognostic profiles, necessitating different therapeutic approaches. Regarding AML patients, we identified that 36% of patients exhibited CIN, with 16% also presenting cytogenetic translocations. Our findings on the prevalence of trisomy 8 and monosomy 7, along with their associated mutations such as *RUNX1* and *ASXL1*, underscore their prognostic significance and the potential need for allogeneic hematopoietic stem cell transplantation (allo-HSCT) in high-risk patients. Additionally, the absence of complex karyotypes in our cohort suggests a more favorable prognosis for these patients. This research underscores the importance of incorporating detailed cytogenetic analysis in the clinical management of AML to improve patient outcomes. These alterations are crucial for risk stratification and treatment planning, emphasizing the need for tailored therapeutic approaches.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: title; Table S1: title; Video S1: title.

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III. DISCUSSÃO GERAL

Este estudo é um dos primeiros a caracterizar o padrão citogenético de pacientes com LLA e LMA de uma população adulta miscegendada do Norte do Brasil. Ele também demonstra como essas alterações de cariótipo podem estar associadas a mudanças em valores hematológicos e bioquímicos, identificando rearranjos cromossômicos recorrentes úteis como uma ferramenta no gerenciamento e acesso aos níveis de risco em pacientes adultos com LMA, juntamente com imunofenotipagem e diagnóstico molecular (Falini *et al*.2023). Além de descrever a instabilidade cromossômica em pacientes adultos com leucemias agudas em uma população mista do Norte do Brasil, destacando o impacto prognóstico dessas alterações citogenéticas em pacientes com LMA e LLA.

III. Capítulo 1. Características hematológicas e bioquímicas associadas a alterações citogenéticas em pacientes adultos com leucemia linfoblástica aguda (LLA) da região norte do Brasil.

Foi observado que nos 50 pacientes com LLA a aneuploidia do cromossomo 21 foi a mais frequente. Esses fenômenos foram observados não apenas em casos de hiperdiploidia e hipodiploidia elevada, mas também em quase todos os casos de LLA haploide (Safavi *et al*., 2017). A conexão entre o cromossomo 21 e a LLA pode ser ainda mais evidente pelo fato de que indivíduos com síndrome de Down apresentam um risco maior de desenvolver LLA-B (Chen *et al*., 2021).

As alterações estruturais citogenéticas observadas com maior incidência entre os pacientes com LLA foram: t(9;22), t(4;11) e t(1;19). O cromossomo Ph (Filadélfia) é formado por uma translocação entre os cromossomos 9 e 22, gerando um gene de fusão que envolve a região 5′ do BCR fundida às sequências 3′ do ABL1 (Sheltzer *et al.,* 2017), uma modificação bem estabelecida em onco-hematologia. Essa descoberta aponta diretamente para a estratégia de tratamento; por exemplo, a adição de inibidores de tirosina quinase (TKIs) *BCR::ABL1* à quimioterapia intensiva melhorou significativamente os resultados para pacientes com leucemia linfoblástica aguda (LLA) positiva para o cromossomo Filadélfia (Ph+). Recentemente, regimes livres de quimioterapia com blinatumomabe e TKIs mostraram resultados excelentes à frente e podem sinalizar uma mudança emergente de paradigma no manejo da LLA Ph+ (Loncarevic *et al*., 1999, Peter *et al*., 2009).

Tal estudo mostra que 6,25% dos pacientes avaliados apresentaram a t(4;11). Essa translocação ocorre em células precursoras do tipo B e são caracterizadas por uma contagem

leucocitária mais alta em comparação com outros subtipos de LLA e um fenótipo imaturo, na maioria dos casos com ausência da expressão de CD10 nas células leucêmicas (Lafage-Pochitaloff et al., 2017; Marks *et al*., 2013). Está associada a um prognóstico desfavorável para pacientes com LLA, bem como a um maior risco de recidiva (Moorman *et al.,* 2007; Chiaretti *et al.,* 2013).

Verificando que os pacientes com t(4;11) apresentam níveis elevados de hemácias e os pacientes com del(9p) apresentaram valores distintos e elevados de parâmetros hematológicos em comparação aos demais pacientes. O produto quimérico *KMT2A::AFF1* se liga e desregula a expressão de genes-alvo essenciais envolvidos na diferenciação de linfócitos, incluindo os genes do cluster homeobox A, *HOXA* e *MEIS1* (Gao *et al*., 2016). A superexpressão de HOXA inibe a eritropoiese e a megacariócitosse, resultando na diminuição dos níveis de hemoglobina e da contagem de plaquetas (Crooks, et al., 1999). Os pacientes deste estudo apresentaram níveis de glóbulos vermelhos abaixo do normal em adultos saudáveis (Sá et al., 2023). Além disso, Zhang e seus colaboradores descreveram que pacientes com leucemia mieloide aguda apresentando t(4;11) tinham a ocorrência simultânea de anemia e trombocitopenia (Zhang et al., 2022), apontando para a influência dessa alteração genética na contagem de glóbulos vermelhos.

Em relação às alterações bioquímicas, observamos que os pacientes com translocações (4;11) e del(6q) apresentaram níveis elevados de uréia em comparação aos demais pacientes, destacando sua relação com alterações renais e prognóstico do paciente. A del(6q) está associada ao desenvolvimento de glomerulosclerose segmentar focal, causando a desregulação da síntese do fator de crescimento endotelial vascular (VEGF) devido à deleção do gene E2F3 (Izu *et al*., 2011).

Em ambas as alterações citogenéticas, a quantidade de ureia está acima dos valores considerados padrões em testes bioquímicos (Adeli *et al*., 2015). A quantidade de ureia é usada para avaliar a função renal, além de o equilíbrio de nitrogênio do corpo ser controlado pela regulação da geração de ureia (Wang *et al*., 2014). A insuficiência renal aguda já foi observada em pacientes com LLA no momento do diagnóstico (Heincelman *et al*., 2016; Rose *et al.,* 2019), onde a taxa de incidência de insuficiência renal em pacientes com LLA não tratada varia de 13% a 25% Munker *et al*., 1998, Luciano *et al*., 2014). Desta forma, a infiltração renal está relacionada a um prognóstico desfavorável em pacientes com LLA (Sherief *et al*., 2015). No entanto, destacamos a necessidade de mais estudos relacionados a t(4;11) e níveis de ureia, uma vez que não observamos estudos associando ambos.

III. Capítulo 2. Uma abordagem citogenética, hematológica e bioquímica em pacientes adultos com leucemia mieloide aguda na região norte do Brasil.

Pela primeira vez, este estudo descreve, citogeneticamente, as alterações cariotípicas em adultos com LMA na região norte do Brasil e sua relação com características hematológicas e bioquímicas. Neste trabalho, cariótipos foram caracterizados em 55 pacientes com LMA da região norte do Brasil, identificando translocações frequentes (por exemplo, t(9;22), t(6;9), t(8;21), t(9;11)). Notavelmente, 14 pacientes apresentaram cariótipo normal. Em nosso estudo, a translocação t(9;22) está presente com uma frequência maior (6%) quando comparada à média global. Essa translocação forma uma oncoproteína de fusão BCR::ABL (Carter *et al*., 2010), sendo classificada como uma entidade rara e provisória para neoplasias mieloides e leucemia aguda pela Organização Mundial da Saúde (OMS) (Arber et al., 2016).

O BCR::ABL é descrito como um grupo de risco adverso na classificação de risco (Döhner et al., 2017). Estudos sugerem a combinação do tratamento com inibidores de tirosina quinase (TKI) e transplante alogênico de células-tronco hematopoéticas (allo-SCT) devido à pobre resposta à terapia tradicional ou ao TKI isoladamente (Lazarevic et al., 2018). No entanto, inibidores mais potentes de BCR::ABL, incluindo dasatinibe, podem ser mais eficazes do que os inibidores anteriores. Eles são eficazes em pacientes idosos com baixa carga tumoral e sem anomalias cromossômicas ou mutações no domínio da quinase ABL que conferem resistência ao tratamento com TKI (Takeuchi et al., 2023).

Observouse que os pacientes com LMA e translocação t(9;22) apresentaram valores médios de eosinófilos (média=1422,9/mm³, DP=34,355, p<0,001), basófilos (média=1,36/mm³, DP=1,51, p=0,001) e bastões (média=5710,4, DP=9890,7, p=0,001) elevados e significativamente diferentes em comparação com outros pacientes com LMA. Provavelmente por consequencia, as contagens de neutrófilos (média=18939/mm³, DP=31820,6, p=0,01) foram mais baixas em comparação com outros pacientes. Modelos hematopoéticos indicam que a expressão da fusão p210 *BCR::ABL* permite exclusivamente o comprometimento e a diferenciação da linhagem mieloide a partir de células-tronco hematopoéticas (HSCs), comprometendo o comprometimento da linhagem linfoide das HSCs através da supressão da transdução de sinal das células B (Zheng *et al*., 2009), o que pode explicar as diferenças nos parâmetros hematológicos encontradas em pacientes com t(9;22).

Os valores de basófilos, eosinófilos e neutrófilos estão acima dos intervalos de referência normais nos parâmetros laboratoriais em pacientes com t(9;22) (Sá et al., 2023). A presença de basofilia é um indicador prognóstico independente na Leucemia Mieloide

Crônica (LMC) Ph+, e há um aumento nos níveis de basófilos à medida que a doença progride, sendo este um critério incluído na maioria dos sistemas de classificação prognóstica para LMC (Hasford *et al., 2011;* , Valent *et al.*, 2018). A importância prognóstica da basofilia foi validada em pacientes tratados com imatinibe ou outros inibidores de BCR::ABL1, sendo um dos fatores de risco mais significativos e bem estabelecidos na LMC (Hasford *et al*., 2011,Sperr *et al., 2015*). O aumento de basófilos e eosinófilos em pacientes com LMA é frequentemente uma situação diagnóstica intrigante que necessita de investigação especial devido à sua relevância clínica (Papadakis *et al*., 2024). Portanto, podemos sugerir que a basofilia encontrada também pode ser um parâmetro prognóstico em pacientes com LMA e t(9;22).

Pacientes com expressão de p210 apresentaram valores médios de potássio significativamente diferentes em comparação com os outros pacientes (p=0,011). Essas médias estão acima dos valores de referência dos marcadores bioquímicos para pessoas saudáveis (Khosrow, *et al*., 2015). Esses valores elevados podem estar relacionados à regulação positiva do canal de potássio dependente de voltagem hEag1 nos pacientes. Na LMA, ele é altamente expresso nos subtipos mais comuns e correlaciona-se com o aumento da idade, maiores taxas de recidiva e menor sobrevida global, sendo um fator preditivo independente de desfechos desfavoráveis (Agarwal et al., 2010). A avaliação do perfil bioquímico ocorre devido à importância do monitoramento nutricional e médico para melhorar a qualidade de vida e a tolerância dos pacientes ao tratamento (Wang et al., 2014).

Destaco que os níveis de glicose em pacientes com t(9;22) e em pacientes do sexo masculino apresentaram médias mais altas em comparação com outros pacientes (p=0,05, p=0,037, respectivamente). Esses valores estão acima dos limites superiores estabelecidos em testes clínicos normais (Khosrow *et al*., 2015). A elevação dos níveis de glicose circulante proporciona às células malignas maior acesso à glicose, criando um ambiente favorável que fornece os nutrientes necessários para o desenvolvimento e crescimento do câncer. Pacientes diabéticos frequentemente têm níveis aumentados de insulina circulante, o que também pode promover o crescimento e a proliferação das células cancerosas (Gallagher et al., 2010).

Da mesma forma, um estudo retrospectivo revelou um aumento na taxa de mortalidade em 30 dias entre pacientes diabéticos, especialmente em adultos mais velhos com leucemia mieloide aguda (LMA) submetido à terapia intensiva. No entanto, no estudo de caso-controle,

não foram encontradas associações entre leucemia, diabetes, sobrevivência e controle glicêmico (Wiedmeier et al., 2020)

III. Capítulo 3. Instabilidade cromossômica em pacientes adultos com leucemias agudas na região norte do brasil.

Nosso estudo destaca o impacto da instabilidade cromossômica em pacientes adultos com leucemia aguda do Norte do Brasil, identificando altas frequências de trissomia 21 e 8 em pacientes com LLA com associações citogenéticas significativas. Em nosso estudo, observamos uma frequência de 6% de trissomia do cromossomo 8. Estudos indicam uma frequência de 10% e um prognóstico desfavorável em pacientes com LLA (Wetzler *et al*.,1999).

Nas malignidades mieloides, a monossomia 7 é a anomalia cromossômica mais comum e está associada a um prognóstico ruim, com uma taxa de sobrevivência global de 0-3% (Inaba et al., 2018). A monossomia 7 também é encontrada em aproximadamente 10% dos casos de LLA de células B precursoras, sendo particularmente comum em casos quase-haplóides, hipodiplóides baixos e positivos para BCR*::ABL*, mas não como uma anomalia isolada de monossomia 7. No entanto, nosso estudo mostrou uma frequência menor em nossa coorte, com a monossomia 7 presente em apenas um paciente com a t(9;22). Da mesma forma, o caso de leucemia linfoblástica aguda granular em um adulto com desfecho clínico desfavorável pode estar associado à variante *DNMT3A* combinada com a monossomia 7 (Lundin-Ström *et al*., 2021).

A del(6q) foi a mais comum entre os pacientes com instabilidade cromossômica, sendo encontrada em 7 dos 50 pacientes com LLA avaliados. Em uma revisão envolvendo 164 casos de LLA com *ETV6::RUNX1*, foi observada uma alta incidência de deleções no 6q (20%) (Lilljebjorn *et al.,* 2010). Na LLA-B, as deleções no 6q que envolvem *FOXO3* e/ou *PRDM1* podem favorecer a sobrevivência da leucemia ao diminuir a sensibilidade à sinalização do receptor de leptina (Sinclair *et al*., 2023).

O *PRDM1* desempenha um papel crucial na regulação da memória das células T humanas, promovendo à exaustão das células T. A interrupção combinada da expressão ou função de PRDM1 e NR4A3 pode gerar células T geneticamente reprogramadas, melhorando as respostas antitumorais imediatas e de longo prazo (Jung *et al*., 2022). A perda da função de *PRDM1/BLIMP-1* está associada a um prognóstico desfavorável em pacientes com linfoma difuso de grandes células B do tipo ativado (ABC) (Xia *et al.* 2024). É importante notar que a

perda de genes como *POU3F2, PRDM13, SIM1* e *FAXC* também pode contribuir para o potencial leucemogênico das grandes deleções 6q, assim como os genes *CCNC e BACH2*, que estão envolvidos em outros subtipos de LLA-B, embora sua função específica nas células B ainda não seja totalmente compreendida (Li *et al*., 2014, Swaminathan *et al*., 2023).

Dentro da coorte do estudo, observamos que a maioria dos casos de hiperploidia sem alterações estruturais estava ligada ao ganho do cromossomo 8, cerca de 0,09%. Proporção semelhante foi encontrada em pacientes com hiperploidia e alterações estruturais. Essa informação é relevante, pois pacientes com apenas alterações citogenéticas numéricas e sem anomalias estruturais têm taxas de sobrevivências melhores comparados àqueles com três ou mais alterações citogenéticas e anomalias estruturais (Chilton *et al.,* 2014).

Identificamos uma frequência de 16% de pacientes adultos com LMA apresentando monossomias, especialmente com a perda do cromossomo 7. Em geral, o cariótipo monossômico tem um prognóstico ruim, mesmo após transplante alogênico de células-tronco hematopoéticas (Breems *et al*. 2008, Kayser *et al.*, 2012).

Não observamos cariótipos complexos (≥ três anomalias cromossômicas não relacionadas na ausência de outras anomalias genéticas recorrentes definidas) no grupo de estudo. Conforme a ICC e a ELN 2022, a classificação de estratificação de risco segue uma hierarquia: LMA com mutação TP53 tem precedência sobre LMA com mutações genéticas relacionadas à mielodisplasia (Döhner *et al*., 2022). Essas alterações são cruciais para a estratificação de risco e planejamento de tratamento, enfatizando a necessidade de abordagens terapêuticas personalizadas em pacientes com Leucemias agudas em adultos.

IV. CONCLUSÃO GERAL

Sendo assim, este é um dos primeiros trabalhos a descrever cariótipo normal, alterações citogenéticas e instabilidade cromossômica em pacientes adultos com leucemias agudas no Norte do Brasil e como tais alterações e cariótipos desempenham um papel crucial no tratamento e prognóstico. Assim como, associar alterações hematológicas e bioquímicas com alterações citogenéticas, cariótipo normal e sexo. Enfatizamos a necessidade de estudos adicionais para validar nossos achados e identificar mais marcadores genéticos associados a desfechos hematológicos e bioquímicos. Uma vez que tais marcadores influenciam significativamente o prognóstico e a estratificação de risco dos pacientes adultos com LLA e LMA.

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Tabela Suplementar 1

Age	Sex	Karyotype	p190	p210	Red blood cells	Hemoglobin	hemató crito	VCM	HCM	CHCM	RDW	Leukocytes	Lymphocytes. relativevalue	Lymphocytes. absolutevalue	Monocyte. relative value	Monocyte. absolute value	Neutrophil. relative value	Neutrophil. absolutevalue	Eosinophil. relative value	Eosinophil. absolutevalue	Basophils. relative values	Basophils. absolute value	Rods. relative value	Rods. absolute value	Erythroblast	platelets	Urea	Transaminase	Creatine	Glucose	Magnesium	Potassium	Sodium
36	M	46, XY	0	0	3.03	8,84	26,3	86,79	29,17	33,61	13,3	760	0	0	0	0	0	0	0	0	0	0	0	0	52	12	49	38	0,97	113	2,29	4,25	138
59	F	46, XX	1	0	1.59	4,61	142	89,3	28,99	32,46	29,6	2.750	45	1.237,5	24	660	23	632,5	0	0	3	82,5	0	0	7	800	29	43	0,75	108	#	#	#
56	M	46, XY	0	0	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#
73	M	46, XY	0	0	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	22	#	#	#	#	#	#	#	#
70	M	46, XY	#	#	2.26	7,19	20,8	92,03	31,81	34,56	15,5	57.400	17	9.758	5	2.870	61	35.014	1	574	0	0	0	0	#	11	27	97	0,96	#	#	4,13	140
86	M	46, XY	#	#	2.78	8,43	27,4	98,56	30,32	30,76	15,2	2.160	65	1.404	5	108	18	3888,8	3,1	66,96	2	43,2	0	0	4	258	51	27	1,29	103	#	#	#

62	M	46,XY	0	0	2.29	6,46	18,8	82,09	28,2	34,36	15,2	1700	55	935	23	391	6	102	0	0	0	0	0	0	12	26	47	14	1	#	#	3,84	135
64	F	46,XX	0	0	3.25	11	30	92,3	33,84	36,66	15,4	1310000	6	7860	1	1310	0	0	0	0	0	0	0	0	29	15	32	25	0,92	42	#	2,8	142
45	M	46,XY	0	0	3.51	11,5	36	102,56	32,76	31,94	14,3	3040	43,1	13110,24	12,5	380	41,5	12611,6	2,6	79,04	0,3	9,12	0	0	38	175	37	23	#	109	1,8	3,1	142
88	F	46,XX	0	0	2.45	6,8	22,6	92,24	27,75	30,08	17,5	323000	7	22261	5	16115	14	45222	0	0	0	0	10	32330	#	26	40	38	1,66	90	1,2	2,8	142
21	M	46,XY	#	#	5.64	14,6	43,1	76,41	25,88	33,87	14,3	41440	36	14990,4	8	331,2	48	19887,2	2	82,8	1	41,4	3	1124,2	#	37	48	13	1,03	102	#	#	#
47	F	46,XX	#	#	3.33	10,4	31,8	95,49	31,23	32,7	16,6	2160	28,7	6199,92	0,5	10,8	62,9	13588,64	7,9	1170,64	0	0	0	0	30,5	23	41	39	1	94	#	#	#
28	F	46,XX	0	0	3.66	11	34,6	94,65	30,05	31,79	23	1900	37	7003	19	361	40	760	1	19	0	0	3	57	34	177	23	71	0,65	113	2	3,3	139
72	M	46,XY	0	0	2.31	8	24,6	106,49	34,63	32,52	0	28220	84	23668,8	3	84,6	8	225,6	0	0	0	0	0	0	12	107	33	11	1,2	118	1,4	#	
43	M	46,XY,t(9;22)	0	0	3.27	9,3	26,1	79,81	28,44	35,63	13,6	50	0	0	0	0	0	0	0	0	0	0	0	0	28	18	59	16		300	1,4	2	138

41	M	48,XY,+8,t(9;22),+12	1	1	4,47	12,7	39	87,24	28,41	32,56	15,3	107070	7	74944,9	3	32121,1	52	55676,4	1	10700,7	3	32122,1	16	171131,2	5	864	24	41	1,24	106	#	5,6	136
28	M	47,XX,t(9;22),+19	1	1	3,11	88	285	91,63	28,29	30,87	24	5330	12,6	671,58	4,9	261,17	21,4	1140,62	60	3198	1,1	58,63	0	0	32	50	18	16	1	96	1,8	#	#
38	M	46,XY,t(6;9)	0	0	2.56	72	209	81,64	28,12	34,44	133	1950	30	585	10	195	12	234	0	0	3	58,5	0	0	30	16	17	12	0,65	104	1,7	4,4	136
40	F	46,XY,t(6;9)	0	0	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	11	#	#	#	#	#	#	#	#
26	M	46,X	#	#	3.17	103	314	990	324	328	179	2450	40	980	13	3188,	46	1127	1	245	0	0	0	0	312	212	20	40	1,05	122	1,5	5	144

		Y,t(9;11)						5	9								5																			
65	M	46,XY,t(9;11)	0	0	2.22	5,4	19,5	87,83	24,32	27,69	18,9	4520	30	1356	3	135,6	64	2892,8	1	45	0	0	1	45,2	35	42	31	18	#	130	2,2	4,5	136
27	F	47,XX+6t(9;11)	#	#	3.32	9,8	31	93,37	29,51	31,61	23	160400	14	22456	7	1122,8	59	9463,6	0	0	0	0	10	1604	39	334	18	27	0,61	#	2,1	3,6	140
41	F	45,XX,-7	0	0	3.96	10,9	34,2	86,36	27,52	31,87	16	18880	38	7144	4	75,2	46	864,8	1	18,8	0	0	1	18,8	50	103	32	14	0,79	100	1,71	#	#
40	F	45,XX,-7	0	0	3.38	7,7	25	73,96	22,78	30,8	15,2	1730	45,1	7800,23	6,4	1101,72	43,3	749,09	5,2	89,96	0	0	0	0	8	186	24	46	0,8	100	1,8	4,3	140
47	F	46,XX,t(8;	#	#	4.14	13,1	39,4	95,16	31,64	33,24	12,9	5060	21,3	10777,78	6,7	3399,02	65,1	3294,06	6,7	339,02	0,2	10,12	0	0	30,5	238	21	19	0,7	105	#	4,6	141

		21)(q22;q22),-7																															
39	M	45,X,-Y,t(8;21)	#	#	1.87	48	145	774	256	331	186	520	0	0	0	0	0	0	0	0	0	0	0	0	0	45	58	37	37	1,15	110	2,15	#	#
24	M	46,XY,t(8;21)	0	0	2.69	76	223	829	285	348	129	3940	31	12211	12	4728	57	2245	0	0	0	0	0	0	0	21	26	28	18	0,93	140	2,2	#	#
20	F	46,XX,t(8;21)	0	0	1.94	61	178	911	314	346	13	1160	534	6194	17	192	449	520	0	0	0	0	0	0	0	4	11	28	9	0,5	78	2,2	3,9	137
19	M	46,XY,i	#	#	2.98	85	255	857	285	333	131	380	0	0	0	0	0	0	0	0	0	0	0	0	0	425	18	109	13	2,75	302	1,88	#	#

		nv(16)(p13q22)																															
57	F	47,XX,inv(16),+8	0	0	31.17	8,6	26,7	84,222	27,112	32,2	13,4	7070	53	37477,1	10	707	7	4944,9	0	0	0	0	0	0	3	42	35	18	#	136	2,4	4,6	136
24	F	47,XX,dup(1q),+8	#	#	33.96	11,3	35,3	89,14	28,53	32,001	18,8	24860	10	24866	6	1491,6	58	14418,8	1	248,6	2	497,2	10	2468	1,5	204	7	20	0,6	83	1,6	2,3	143
59	M	46,XY,t(10;11)	0	0	2	5,9	18,2	91	29,5	32,41	15,6	120060	15	18009	3	361,8	4	4824	0	0	0	0	0	0	#	10	49	58	#	84	1,8	4,3	130
40	M	46	0	0	2.	8,	24	82	28	34	14	41	32	13	16	65	8	32	0	0	0	0	11	45	4	32	47	12	#	13	2,	3,	13

		,XY,inv(3q),t(7;111),t(12;13)			99	5	,8	,94	,42	,27	,8	00		12		6		8						1						4	3	9	9
27	F	46,XX,del(7q)	1	1	3,42	9,1	28,1	82,16	26,6	32,38	16,5	4290	22	943,8	1	42,9	74	3174,6	0	0	2	85,8	1	42,9	24	385	12	12	0,75	85	1,4	4,7	139
59	M	46,XY,del(7)(q22q34)	0	0	2,11	6,16	17,6	83,41	29,19	35	14,3	1870	72	1346	4	74,8	1	18,7	1	18,7	0	0	0	0	7	14	35	12	0,9	123	2,5	4,1	135
#	M	4	0	0	2	6	2	9	3	3	1	4	3	1	1	4	0	0	0	0	0	0	0	0	4	1	3	2	1	*	2	4	1

		5,X,-Y,del(7)(q11.2),t(8;2)(q22;q22),-9,+mar			,17	,92	1,4	8,61	1,88	2,33	7,1	4.500		.335		45										8	6	4	4	,2			,08	37
62	M	43,-X,Y,-7,-21	#	#	2.66	7,9	24,9	93,6	29,69	31,72	17,1	660	0	0	0	0	0	0	0	0	0	0	0	0	20,7	52	24	16	0,62	136	2,1	2,8	130
64	M	45,X	#	#	3.04	92,	304,	100	302,	302,	0	910	55	500,	3	273,	25	227,	16	145,	0	0	1	91,	56	29	58	12	1,4	134	2,2	3,1	143

		,-Y,dup(11q)							6	6				5				5		6																
45	F	46,XX,t(1;2)	#	#	46.26	13,6	37,5	88,02	31,92	36,26	12,4	5970	28,3	16889,51	9,9	591,03	58,9	35116,33	2,7	1611,19	0,2	11,94	0	0	48,2	159	34	69	0,74	152	1,8	#	#
49	F	45,XX,t(3;3),t(5;12),-7	0	0	31.31	10,11	32,4	97,88	30,51	31,17	22,6	6050	16	968	10	605	74	4477	0	0	0	0	0	0	0	35,5	324	21	11	0,5	74	1,9	#	#
59	F	46,XX,t(3;21),-7,+1	0	0	2.73	9	26,8	98,16	32,96	33,58	20,6	610	73,8	4500,18	3,3	20,13	13,1	79,91	9,8	59,78	0	0	0	0	27	144	13	9	0,5	88	0,89	#	#

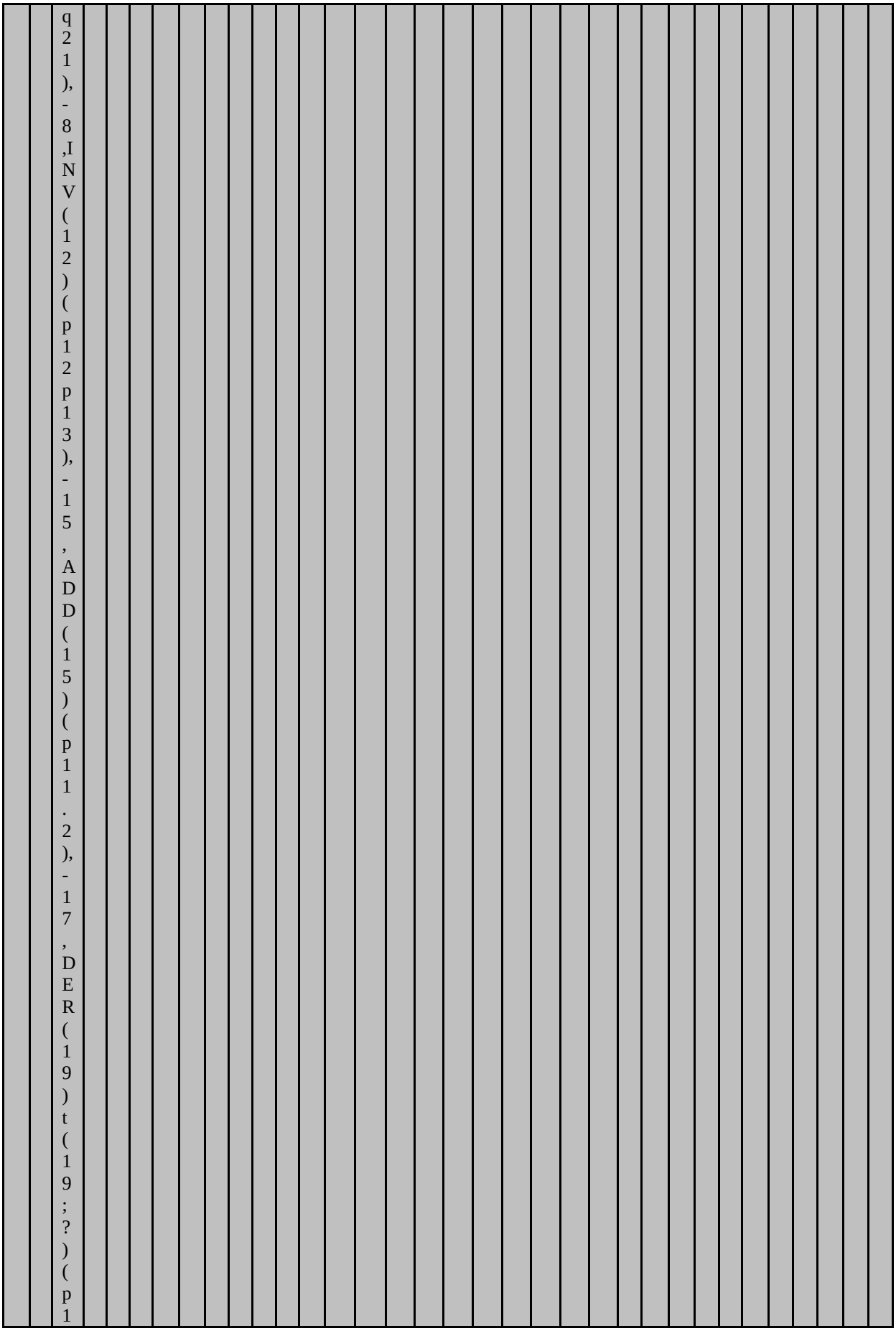
		2																														
29	M	47,XY,+8,t(15;17)	0	0	2.94	86,6	259,9	888,09	292,25	333,2	16,7	213220	12	25584,4	5	1066	5	1066	0	0	0	0	0	0	0	245,5	150	26	17	0,8	93	2,3	4	143
42	M	46,XY,t(1;16)(q12;24),t(15;17)(q24;q21)	*	*	2.12	66,27	173,3	816,6	299,57	366,24	12,6	97.200	4	3.888	1	972	5	4860	0	0	0	0	0	0	0	*	16	36	41	0,84	155	2,51	3,5	138
41	M	46,XY,t	0	0	41.73	149,9	424,4	899,64	315,5	355,14	12,4	6430	30	1929	12	771,6	44	2829,2	13	835,9	0	0	1	64,3	384,4	301	25	260	0,8	91	2,5	4,2	144

		(4;11),i(7q)																														
28	F	45,XX,inv(3q),i(7),-17	0	0	1.9	6,1	18,8	98,94	32,1	32,44	24,5	108850	5	54425	28	30478	8	8708	0	0	0	0	1	10885	#	19	149	14	4,2	32	2,38	#	#
57	M	45,XY,-5,del(12P)	0	0	2.87	8,1	24,9	86,75	28,22	32,53	18,3	138780	12	166653,6	1	13887,8	8	11102,4	0	0	0	0	1	13887,8	25	78	144	11	6,02	21	2,32	#	#
44	F	47,XX,del(5q).+	#	#	4	11,8	35,9	89,75	29,5	32,86	14,5	4930	29,2	14439,56	8,1	399,33	61,1	30123,23	1,4	69,02	0,2	9,86	0	0	7	204	27	23	#	98	2,4	4,6	138

		8																													
60	F	46,X,der(X)t(x,?)(q24;?),del(5)(q31q35),t(8;21)(q22;q22)	#	#	2.8	8,53	24,2	86,42	30,46	35,24	14,1	11.7000	35	4.0095	6	702	18	2.106	1	117	0	0	0	0	49	9	44	12	0,6	116	*	3,39	139
22	F	47,XX	0	0	3.01	9,83	26,9	89,36	32,65	36,54	17,8	43900	6	2634	1	439	1	439	0	0	0	0	0	0	3	130	8	25	0,43	105	#	3,74	137

		,+8																																
27	M	47,XY,+8{14}/46,XY{6}	0	0	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#
25	M	47,XY,+21	0	0	2,11	5,81	17,9	84,83	27,53	32,45	13,1	4340	42	18222,8	5	217	35	1519	0	0	0	0	0	0	40	9	48	19	0,86	*	*	3,2	135
30	M	49,XY,+9,+21,/46,XY	0	0	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#
56	M	46,XY,t(3	0	0	2,34	6,22	20	85,47	26,58	31,1	13,3	5.760	31	1.7850,60	23	1.3240,80	22	1.2667,20	0	0	0	0	7	4003,2	#	7	30	#	0,73	#	#	4,15	135

		;7)(p25;q22)/46,XY																																
#	F	46,XX,t(3;5)(q21;q31)	0	0	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#
71	M	43-44,XY,-5,DEL(6)(q15	0	0	1,95	5,34	16,6	85,12	27,38	32,16	13,2	6.820	41	2.796,20	4	272,8	12	818,4	0	0	0	0	6	409,2	5	5	#	#	#	#	#	#	#	#


q21),-8,INV(12)(p12p13),-15,ADD(15)(p11.2),-17,DER(19)t(19;?)(p1

		3;?),-21,-22,+MAR1,+MAR2,+R[CP20]																																		
59	F	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#	#
Information																																				
#=missingdata																																				
1=positi																																				

ve																															
0 = negative																															

Tabela Suplemenar Capítulo 3

Tabela com os cariótipos de pacientes com LLA.

IDADE	SEXO	CARIÓTIPO
35	F	46,XX, t(4;11)(q21;q23)
51	F	47, XX,t(4;11) + 8
51	M	46, XY, t(4;11).
33	M	46,XY, t(9;22)
26	M	47, XY,t(9;22),+21.
28	M	46, XY, t(9;22)
54	M	46, XY,t(9;22)
44	M	46, XY, t(9;22)
47	M	46, t(9;22);
31	M	46, XY, t (9;22)
29	M	47, XY, t(9;22), +21
17	M	47, XY, t (9;22), +21
29	M	48, XY, t(9;22),+der(22),+21
37	F	47, XX, der(7)t(1;7), t(9;22), +21
31	F	50,XX, +4, t(9;22), t(12;21), +14, +18, +21
61	F	46, XX, del(6q), t(9;22)
39	F	46,XX, t(9;22)(q34.1;q11.2)-7,der(1;7)(p10;q10),add(11)(q25),+mar1,+mar2,mar+3,mar4[5]
28	F	46,XY,t(9;22) (q34.1;q11.2)
20	M	48,XY, t(1;19), +8, +21
18	F	47,XX,t(1;19),i(17q),+21
21	M	47, XY, t(1;19), del(6q) +21
35	M	46, XY, t(1;19), del(9p)
25	F	47, XX, +5, del(6q)
24	F	46, XX, del(6q).
31	M	49, XY,+4, del(6q), +6, +10, del(12p), -13, +18
40	F	44, XX,del(6q), del(12q), -13, -17
37	M	46, XY, del(5q), del(6q)e del(12p).
19	F	46, XX, -7, del(9p), +21
46	M	46, XY, del(9p)
62	M	46, XY, del(9p), del(13q), +21
31	F	47, XX, i(9q), +21
34	M	46, XY, t(6;12), i(9q)

45	M	46, XY
25	M	46, XY
43	F	46,XX
20	M	46,XY
46	M	46, XY.
46	F	46.XX
20	M	49, XY, +3, +8, t(10;14)(q24;q11), -12, +14, -17,+21,+22
54	F	42, XX, -X, -6, del(12p), -13, -17
33	F	47, XX, del(1q), +der(7)t(7;19), -19, +21
47	F	48, XX, trp(1q), t(3;12), -7, +13, +13
20	F	48, XX,+16, +21
58	M	46, XY, t(14;17)
22	M	46,XY,t(8;13)
20	M	46, XY, t(1;14)
18	M	47 XY, t(10;14), +20
36	M	46, XY, t(6;12), i(9q)
26	M	47,XY,t(12;21), +21
19	F	47, XX +21

Tabela com os cariótipos dos pacientes com LMA.

Idade	Sexo	Cariótipo
36	M	46,XY
59	F	46, XX
56	M	46,XY
73	M	46,XY
70	M	46,XY
86	M	46,XY
62	M	46,XY
64	F	46,XX
45	M	46, XY
88	F	46,XX
21	M	46,XY
47	F	46, XX
28	F	46,XX
72	M	46,XY
43	M	46, XY,t(9;22)
41	M	48,XY,+8, t(9;22), +12
28	M	47,XX,t(9;22),+19
38	M	46,XY,t(6;9)
40	F	46,XY,t(6;9)
26	M	46, XY, t(9;11)
65	M	46, XY,t(9;11)
27	F	47, XX +6 t(9;11)
41	F	45,XX,-7
40	F	45,XX,-7
47	F	46, XX, t(8;21)(q22;q22), -7

39	M	45, X, -Y, t(8;21)
24	M	46,XY,t(8;21)
20	F	46,XX,t(8;21)
19	M	46, XY, inv(16)(p13q22)
57	F	47, XX, inv (16), +8
24	F	47, XX, dup(1q), +8
59	M	46, XY, t(10;11)
40	M	46, XY, inv(3q), t(7;11), t(12;13)
27	F	46, XX, del(7q)
59	M	46,XY, del(7) (q22q34)
#	M	45,X, -Y,del(7) (q11.2), t(8;2) (q22;q22), -9, +mar
62	M	43, -X, Y, -7, -21
64	M	45, X, -Y, dup(11q)
45	F	46,XX,t(1;2)
49	F	45,XX,t(3;3),t(5;12),-7
59	F	46,XX,t(3;21),-7,+12
29	M	47,XY,+8,t(15;17)

42	M	46,XY,t(1;16) (q12;24), t(15;17)(q24;q21)
41	M	46,XY,t(4;11),i(7q)
28	F	45,XX,inv(3q),i(7),-17
57	M	45,XY,-5,del(12P)
44	F	47,XX, del(5q). +8
60	F	46,X,der(X) t(x,?) (q24;?), del(5) (q31q35), t(8;21) (q22;q22)
22	F	47,XX,+8
27	M	47,XY,+8{14}/46,XY{6}
25	M	47,XY,+21
30	M	49,XY,+9,+21,/46,XY
56	M	46,XY, t(3;7) (p25;q22)/46,XY
#	F	46,XX, t(3;5) (q21;q31)

71	M	43-44,XY,-5,DEL(6) (q15q21),-8,INV(12) (p12p13), -15,ADD(15) (p11.2), -17, DER(19) t(19;?) (p13;?), -21,-22, +MAR1,+MAR2, +R[CP20]

COMITÊ DE ÉTICA

HOSPITAL OPHIR LOYOLA - HOL

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ANALISE CITOGENÉTICA DE PACIENTES COM LEUCEMIAS AGUDAS NO NORTE DO BRASIL E IMPACTO NO PROGNOSTICO

Pesquisador: Rommel Mario Rodriguez Burbano

Área Temática: Genética Humana:
(Trata-se de pesquisa envolvendo Genética Humana que não necessita de análise ética por parte da CONEP;);

Versão: 1

CAAE: 39611320.0.0000.5550

Instituição Proponente: Hospital Ophir Loyola

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.409.317

Apresentação do Projeto:

Este estudo irá descrever as alterações cromossômicas dos pacientes adultos com as

LA no Norte do Brasil, e tais informações poderão servir como um norte no tratamento dos pacientes, uma vez que alterações citogenéticas específicas e ainda fornecer informações que podem influenciar diretamente no prognostico em resposta ao tratamento das LA.

Serão avaliados dados citogenéticos (no caso cariótipos), alterações moleculares, perfil hematológicos, perfil lipídico, Recidiva (retorno da doença após tratamento inicial), Sobrevida global (período durante o qual um paciente permanece

vivo após o diagnóstico da doença ou início do tratamento) e sobrevida livre de doença (período em que não se detectam sinais nem sintomas

da doença após um tratamento curativo) dos pacientes diagnosticados com Leucemias Agudas presente no banco de dados, do laboratório de Biologia Molecular do Hospital Ophir Loyola.

Será utilizado o TCUD (ANEXADO NO PROJETO)

Objetivo da Pesquisa:

O Objetivo deste estudo é descrever o perfil citogenético e molecular dos pacientes adultos com leucemia aguda no Norte do Brasil, e sua relação com os prognósticos dos pacientes ao longo do tratamento.

Continuação do Parecer: 4.409.317

Avaliação dos Riscos e Benefícios:

Riscos:

Serão tomadas todas as providências para que não haja divulgação de informações pessoais dos pacientes e que eles não sejam identificados.

Benefícios:

Descrevendo as alterações citogenéticas dos pacientes adultos com as LA da região norte do Brasil e as associar com os dados do perfil lipídico e hematológico, mortalidade e remissa da doença (no caso o prognostico do paciente),podemos assim, compreender melhor a biologia da doença e desenvolver um protocolo de tratamento mais especifico, que possibilite apresentar uma reposta no tratamento de maneira mais eficaz conforme as características biológicas dos pacientes com LA da região norte do Brasil.

Comentários e Considerações sobre a Pesquisa:

A referida pesquisa será de importante relevância para o universo científico.

Considerações sobre os Termos de apresentação obrigatória:

Anexar o cronograma da pesquisa.

Recomendações:

Anexar o cronograma da pesquisa.

Conclusões ou Pendências e Lista de Inadequações:

Sem pendências

Considerações Finais a critério do CEP:

Conforme Res. CNS 466/12, a responsabilidade do pesquisador é indelegável e indeclinável e compreende os aspectos éticos e legais da pesquisa. Nesse sentido, ressaltamos as seguintes atribuições do pesquisador:

- Em se tratando de projetos a serem desenvolvidos no Hospital Ophir Loyola - HOL, os pesquisadores devem apresentar o parecer de aprovação emitido pelo CEP, junto a Divisão de Pesquisa do HOL, antes de iniciar a pesquisa;
- Desenvolver o projeto conforme delineado;
- Elaborar e apresentar os relatórios parcial (is) e final;
- Apresentar dados solicitados pelo CEP ou pela CONEP a qualquer momento;
- Manter os dados da pesquisa em arquivo, físico ou digital, sob sua guarda responsabilidade, por um período de 5 (cinco) anos após o término da pesquisa;
- Encaminhar os resultados da pesquisa para publicação, com os devidos créditos aos

pesquisadores associados e ao pessoal técnico integrante do projeto e
- Justificar fundamentadamente, perante o CEP ou a CONEP, interrupção do projeto ou a não publicação dos resultados.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Outros	Fr_novo.pdf	27/10/2020 15:54:01	SHERMAINE ANASTACIA SILVA MARQUES THIJM	Aceito
Declaração de Instituição e Infraestrutura	Declaracao.pdf	27/10/2020 15:12:14	SHERMAINE ANASTACIA SILVA MARQUES THIJM	Aceito
Outros	iniciacao.pdf	27/10/2020 15:10:57	SHERMAINE ANASTACIA SILVA MARQUES THIJM	Aceito
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1631543.pdf	20/10/2020 15:28:31		Aceito
Projeto Detalhado / Brochura Investigador	projeto_detalhado.pdf	20/10/2020 15:26:21	Rommel Mario Rodriguez Burbano	Aceito
Outros	ISENCAO_DE_ONUS.pdf	20/10/2020 15:19:23	Rommel Mario Rodriguez Burbano	Aceito
Outros	TCUD.pdf	20/10/2020 15:17:44	Rommel Mario Rodriguez Burbano	Aceito
Declaração de concordância	anuencia_de_orientacao.pdf	20/10/2020 15:16:34	Rommel Mario Rodriguez Burbano	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	dispensa.pdf	20/10/2020 15:13:27	Rommel Mario Rodriguez Burbano	Aceito
Folha de Rosto	FOLHA.pdf	16/10/2020 16:03:57	Rommel Mario Rodriguez Burbano	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não