UNIVERSIDADE FEDERAL DE SERGIPE
CENTRO DE CIÊNCIAS BIOLÓGICAS E DA SAÚDE
DEPARTAMENTO DE MEDICINA

WALLACE MARCELO ALMEIDA SILVA

MANIFESTAÇÕES OCULARES EM PACIENTES PEDIÁTRICOS COM LEUCEMIA LINFOBLÁSTICA AGUDA: UMA COORTE DE CINCO ANOS

Aracaju/SE

2019

WALLACE MARCELO ALMEIDA SILVA

MANIFESTAÇÕES OCULARES EM PACIENTES PEDIÁTRICOS COM LEUCEMIA LINFOBLÁSTICA AGUDA: UMA COORTE DE CINCO ANOS

Trabalho de conclusão de curso apresentado ao Departamento de Medicina da Universidade Federal de Sergipe como requisito parcial para obtenção do título de Bacharel em Medicina

Orientadora: Profª. PhD. Rosana Cipolotti

Aracaju/SE

2019

Wallace Marcelo Almeida Silva

MANIFESTAÇÕES OCULARES EM PACIENTES PEDIÁTRICOS COM LEUCEMIA LINFOBLÁSTICA AGUDA: UMA COORTE DE CINCO ANOS

Trabalho de conclusão de curso apresentado ao Departamento de Medicina da Universidade Federal de Sergipe como requisito parcial para obtenção do título de Bacharel em Medicina

Autor: Wallace Marcelo Almeida Silva

Orientadora: Profª. PhD. Rosana Cipolotti

Wallace Marcelo Almeida Silva

MANIFESTAÇÕES OCULARES EM PACIENTES PEDIÁTRICOS COM LEUCEMIA LINFOBLÁSTICA AGUDA: UMA COORTE DE CINCO ANOS

Trabalho de conclusão de curso apresentado ao Departamento de Medicina da Universidade Federal de Sergipe como requisito parcial para obtenção do título de Bacharel em Medicina

Aprovado em: _____de_____de _____

Banca examinadora:

_____

Universidade Federal de Sergipe

_____

Universidade Federal de Sergipe

_____

Universidade Federal de Sergipe

Dedicatória

Aos pacientes do Centro de Oncologia de Sergipe Dr. Oswaldo Leite, em especial a Matheus Prazeres *(in memoriam).*

LISTA DE ABREVIAÇÕES

AR	Alto risco de recaída da doença
BR	Baixo risco de recaída da doença
GC	Glicocorticóides
GR	Gen receptor de glicocorticoide (GR-NR3C1)
HO	Hipertensão Ocular
LLA	Leucemia Linfoblástica Aguda
MO	Manifestações oculares
MMP_2	Matriz de metaloproteinase-2
PIO	Pressão intraocular
POAG	Glaucoma primário de ângulo aberto
TM	Malha trabecular do ângulo da câmara anterior ocular
TPA	Ativador do plasminogênio tecidual

SUMÁRIO

1. INTRODUÇÃO 7
2. REVISÃO DE LITERATURA 8
2.1 Manifestações Oculares 10
2.1.1 Manifestações primárias 10
2.1.2 Manifestações Secundárias 12
2.1.3 Glaucoma Cortisônico e Hipertensão Ocular 13
3. REFERÊNCIAS BIBLIOGRÁFICAS 17
4. REGRAS PARA PUBLICAÇÃO 28
5. ARTIGO ..... Erro! Indicador não definido.

1. INTRODUÇÃO

A leucemia linfoblástica aguda (LLA) é, na faixa pediátrica, o câncer mais comum e responde por aproximadamente 26% dos casos de câncer infantil (WARD et al., 2014) . A LLA corresponde a 80% dos casos diagnosticados em pacientes de zero a 14 anos e aproximadamente 56% dos casos em adolescentes acima dos 14 anos. Nos últimos 30 anos, os avanços científicos se traduziram em melhorias nas propostas terapêuticas que culminaram numa redução da mortalidade por LLA em mais de 30% (WARD et al., 2014). Atualmente tais pacientes possuem, em média, sobrevida livre de doença de até 90% em cinco anos (WARD et al., 2014; MARCOUX et al., 2016).

Apesar do sucesso do tratamento quimioterápico para LLA, vários estudos apontam para alterações tardias em diversos órgãos e sistemas, incluindo os domínios emocionais e cognitivos (ALLEMANI et al., 2015; BERBIS et al., 2014; HONG et al., 2014; MERTENS et al., 2014; WHELAN et al., 2010). As lesões oculares e orbitais são a terceira manifestação extramedular mais comum da LLA, depois das lesões meníngeas e testiculares, variando entre 43 a 90% dos casos (CHARIF et al, 2002, TALCOTT; GARG; GARG, 2016; SHARMA et al., 2004).

As manifestações oculares (MO) tanto podem estar relacionadas à infiltração direta do olho e da órbita pelas células neoplásicas, quanto serem secundárias à anormalidades vasculares tumor-induzida ou a complicações pelo uso de medicamentos quimioterápicos, incluindo altas doses de glicicorticoides (GC) (RAZEGHINEJAD; KATZ, 2012; MENDONCA et al, 2014).

Por se tratar de uma doença oncológica com grande potencial de cura e que compromete indivíduos com elevada expectativa de vida, é importante caracterizar as MO de pacientes pediátricos em tratamento para LLA, bem como avaliar se tais manifestações possuem correlação com preditores de risco de recidiva definidos na literatura e outros fatores como protocolo de tratamento quimioterápico, idade, gênero, óbito, imunofenotipagem e infiltração do liquor por células neoplásicas. Identificar e tratar precocemente tais alterações oculares pode prevenir dano permanente à visão, além de diagnosticar precocemente uma possível infiltração ou recidiva incipiente da doença.

2. REVISÃO DE LITERATURA

A LLA constitui 26% de todas as neoplasias em indivíduos de zero a 15 anos, constituindo 80% das leucemias infantis. Seu pico de incidência ocorre entre dois e cinco anos de idade, com média de idade de 6,5 anos, sendo discretamente mais frequente no sexo masculino, em indivíduos de cor branca e de países desenvolvidos (WARD et al., 2014; YEOH et al., 2013; YOUNG et al., 1986). História familiar está presente em 5% dos casos (YASMEEN; ASHRAF, 2009; YOUNG et al., 1986).

As taxas de leucemia linfoide variaram cerca de 10 vezes entre 54 populações estudadas, sendo mais elevadas em hispânicos brancos dos EUA, seguidas pelo Equador, e sendo mais baixas na população negra dos EUA, Tunísia e Uganda. Essa variação quanto à distribuição geográfica pode ser atribuída a fatores de risco ambientais, genética e/ou diferenças nos critérios de diagnóstico e no tratamento (LINET MS et al., 2015). Estudos epidemiológicos de câncer na América do Sul não são comumente relatados. A mediana da taxa de incidência ajustada de leucemia no Brasil e na Argentina foi de 47 por milhão (DE CAMARGO et al., 2010; MORENO F et al., 2013). No Brasil, em Recife-PE, estudo estimou em cerca de 48,5 casos por milhão de crianças e adolescentes (LINS et al., 2016).

Em virtude dos avanços no tratamento, a taxa de mortalidade da LLA declinou mais de 30% nos últimos 30 anos (WARD et al., 2014). Por se tratar de uma neoplasia maligna das células precursoras de linfócitos, caracterizada pela aberração na proliferação e diferenciação dos precursores linfoides, a LLA acarreta falência do sistema imunológico e decréscimo na hematopoese normal, resultando em anemia, trombocitopenia e neutropenia. É comum ao exame a presença de anemia (86%), linfadenopatia (75%), hepatomegalia (67%) e esplenomegalia (58%). Inicialmente pode haver leucocitose elevada (>50.000), observada em 34% dos pacientes, hemoglobina <7g/dl em 54%, plaquetopenia <20.000 em 33% e comprometimento de sistema nervoso central em 5% (YASMEEN; ASHRAF, 2009).

Os pacientes são classificados no momento do diagnóstico em dois grupos, de acordo com o risco de recidiva. Os pacientes com alto risco de recaída (AR) são aqueles que preencheram um dos seguintes critérios: idade igual ou superior a nove anos, contagem de leucócitos maior que ou igual a 50.000 células/mm^3 no momento do diagnóstico e imunofenotipagem compatível com LLA de células T. O grupo de baixo risco (BR) engloba os pacientes que não preenchem nenhum dos critérios acima (CERDÀ-IBÁÑEZ et al., 2018).

Existem diferenças notáveis entre os países de baixa e média renda em comparação com os países desenvolvidos em relação aos índices de mortalidade durante a indução, mortalidade aos seis meses após o diagnóstico (início da fase de manutenção), infiltração no líquido cefalorraquidiano e proporção de pacientes de alto risco de recaída. Essas diferenças estão mais diretamente relacionadas ao acesso à infraestrutura adequada para o tratamento de complicações do que aos aspectos biológicos da doença (HOWARD et al., 2008).

Hoje, nos países desenvolvidos, uma criança com diagnóstico de LLA tem uma expectativa de sobrevida média em cinco anos de até 90% com 95% de probabilidade de viver mais 10 anos passados os cinco iniciais (WARD et al., 2014; MARCOUX et al., 2016). A Sociedade Americana de Câncer mostra que em 2016, 6590 novos casos foram diagnosticados com 1400 mortes secundárias à LLA (TERWILLIGER; ABDUL-HAY, 2017).

O tratamento consiste em quatro a seis semanas de quimioterapia de indução inicialmente administrada no hospital, seguida por vários meses de quimioterapia de consolidação (geralmente até os seis meses do início do tratamento) e dois a três anos de quimioterapia de manutenção (MARGOLIN et al., 2010). Os mais recentes protocolos de tratamento da LLA utilizados no Brasil foram propostos em 1999 e atualizados em 2009 (ALL-99 e ALL-09) pelo "Grupo Brasileiro de Tratamento da Leucemia Linfoblástica Aguda na Infância" da Sociedade Brasileira de Oncologia Pediátrica. Ao final dos primeiros 28 dias de tratamento (D28) o protocolo ALL-99 previa uma dosagem total de 1120 mg/m^2 de Prednisona para o grupo BR e 1680 mg/m^2 de Prednisona para o grupo AR. O protocolo ALL-09 previa 420 mg/m^2 de prednisona e 126 mg/m^2 de dexametasona para o grupo BR e 1260 mg/m^2 de prednisona para o grupo AR (BRANDALISE et al., 2010; WATANABE, 2007).

Apesar do sucesso do tratamento quimioterápico para LLA, vários estudos apontam para alterações tardias em diversos órgãos e sistemas, incluindo os domínios emocional e cognitivo, deficiência de crescimento, risco aumentado para o aparecimento de novo câncer como Leucemia Mieloide Aguda ou Linfoma, tumor de sistema nervoso central e pescoço (BERBIS et al., 2014; HONG et al., 2014; MERTENS et al., 2014; WARD et al., 2014; WHELAN et al., 2010). Lesões oculares e orbitais são a terceira manifestação extra medular mais comum da leucemia aguda, depois das lesões meníngeas e testiculares (CHARIF et al, 2002; GORDON et al, 2001).

2.1 Manifestações Oculares

De maneira geral, a fisiopatologia do acometimento ocular na LLA deve-se a três mecanismos principais: I) infiltração direta do olho e órbita pelas células neoplásicas; II) anormalidades vasculares afetando a retina ou III) acometimento neuro-oftalmológico (REDDY; MENON, 1998). No primeiro caso pode-se ter invasão de coroide, hifema, hipópio, heterocromia da íris, glaucoma secundário, proptose, episclerite (YALCINBAYIR et al., 2017; ÇAÇA et al., 2005); no segundo, hemorragias retinianas, manchas de Roth, exsudatos algodonosos, oclusões vasculares, descolamento de retina, microaneurismas, dilatação e tortuosidade venosa (YALCINBAYIR et al., 2017; SHARMA et al., 2004; ÇAÇA et al., 2005; CHAUDHURI; ROY; ROY, 2013); no terceiro, a infiltração do nervo óptico pode acarretar paralisia de nervos cranianos e papiledema (SHARMA et al., 2004). Entre as anormalidades retinianas, uma revisão observou 24% de hemorragias retinianas, 11% de manchas de Roth e 16% de exsudatos (TALCOTT; GARG; GARG, 2016). Mais frequente parece ser a infiltração da coroide, estimada em 50 a 82% dos casos (GORDON et al., 2001).

Envolvimento ocular pode ser classificado em duas principais categorias: primária ou infiltração leucêmica direta, e secundária ou envolvimento indireto (SHARMA et al, 2004). A infiltração leucêmica direta pode ser observada em três diferentes padrões: (a) infiltração uveal, infiltração orbital, e sinais neuro-oftalmológicos de infiltração nervosa (CHAUDHURI et al, 2013; LIN H-F et al, 2005), (b) paralisia de nervos cranianos e (c) papiledema (NGUYEN et al, 2013). As alterações secundárias são manifestações retinianas, hemorragia vítrea, infecções, e oclusões vasculares devido as anormalidades hematológicas da leucemia como anemia, trombocitopenia, hiperviscosidade e imunodepressão (SHUYUAN LYU et al, 2018).

2.1.1 Manifestações primárias

A córnea é uma estrutura avascular e, portanto, não é comumente envolvida na leucemia, especialmente na forma de invasão de direta de células leucêmicas. Pode haver envolvimento da córnea além do envolvimento do limbo (ALLEN, 1961). Alterações corneanas são também vistas quando o seu epitélio se transforma devido ao tratamento quimioterápico. Essas mudanças incluem adelgaçamento irregular, maturação defeituosa e queratinização (JABS et al, 1983). Apesar de o envolvimento da conjuntiva não ser uma

apresentação comum da leucemia, ocorre mais comumente em pacientes em leucemias linfoides (DUKE, 1965).

Infiltração da esclera é geralmente um achado de autópsia e ocorre em leucemias agudas. Essas células são achadas mais frequentemente na episclera em um padrão perivascular (ALLEN et al, 1961).

Clinicamente, infiltração evidente da íris por células leucêmicas não é comum. Isso ocorre com o envolvimento da coroide e do corpo ciliar e é clinicamente caracterizado por mudança na cor da íris e um pseudohipópio, de coloração cinza/amarelada (PERRYet al, 1979). Leucemias foram identificadas como a doença de base em 5% dos casos de uveítes na pediatria (SOYLU et al,1997).

A coroide demonstra infiltração leucêmica mais consistentemente no exame histopatológico, embora, clinicamente, a retina seja a parte mais envolvida na leucemia. O envolvimento da coroide por células leucêmicas tende a ser perivascular e desigual ou difuso (ALLEN et al, 1961).

A retina é o tecido ocular mais envolvido na leucemia. É estimado que até 69% de todos os pacientes com leucemia mostram alteração de fundo de olho em algum ponto durante o curso da doença. (ALEMAYEHU et al, 1996) As manifestações precoces, por conta dos distúrbios hematológicos, são dilatação e tortuosidade venosa. (BALLANTYNE et al,1970) As hemorragias e infiltrações são vistas em todos os níveis da retina, especialmente nas camadas interiores com destruição focal. Os infiltrados e agregados de células leucêmicas são geralmente vistos em torno das áreas hemorrágicas. A membrana limitante interna frequentemente atua como uma eficiente barreira contra a infiltração de células leucêmicas. (KUWUBARA; AIELLO,1964). Contudo, células leucêmicas ocasionalmente invadem o vítreo possivelmente emergindo da cabeça do nervo óptico (REESE et al, 1976).

Como consequência do aumento na sobrevida, o envolvimento do sistema nervoso e do nervo óptico se tornou mais frequente, particularmente na leucemia aguda. Pode aparecer, mesmo quando a medula óssea está em remissão, já que a barreira hematoencefálica restringe a livre passagem de certos agentes quimioterápicos (SHAW et al,1960; RIDGWAY, 1976). Infiltração do sistema nervoso central ocorre tanto em adulto, menos comum, quanto em crianças (DAWSON, 1973) e mais comumente em LLA comparado às Leucemias Mieloides Agudas (HYMAN, 1965).

Infiltração orbital na leucemia se apresenta como exoftalmia, edema palpebral e dor (COLOMBINI A et al, 1995; CAVDAR AO et al, 1971). Todos os tipos de leucemia podem atingir a órbita, porém o envolvimento orbital é mais comum nas leucemias agudas

comparadas as crônicas e ocorrem mais comumente em leucemias linfoides quando comparas as mielóides (JAKOBIEC, 1979).

Outras alterações oculares menos comuns da leucemia incluem necrose do segmento anterior, dacriocistite e infiltração da pele (CULLIS et al, 1952).

2.1.2 Manifestações Secundárias

Pacientes com leucemia, durante o período de neutropenia, são mais suscetíveis a desenvolver infecções incomuns e que ameacem a vida. Esses pacientes são suscetíveis a uma ampla variedade de infecções virais, fúngicas, bacterianas e de protozoários (COGAN, 1977). Uma das infecções mais comuns nos imunocomprometidos é por citomegalovírus (CMV) (SHIBATA, 1997), que invade a retina, causando necrose, hemorragia, e combina descolamento exsudativo e regmatogênico da retina (MEREDITH, 1979). Outros vírus (herpes simples, varicela zoster e caxumba) também podem causar retinite necrotizante em pacientes imunocomprometidos (COGAN, 1977). Herpes zoster também pode causar úlcera corneal periférica, ceratite e esclerite (WALTON, 1999).

Os fungos são a causa mais comum de infecções oculares nas leucemias. Infecção por Candida causa uveíte e retinite com infiltratos algodonosos no vítreo. Outra infecção fúngica comum em pacientes com leucemia é por Aspergillus (COGAN, 1977).

Infecção bacterina por Pseudomonas é comum em pacientes imunossuprimidos. Essa infecção pode iniciar como blefaroconjutivite e se estender causando celulite orbitária (GIAGOUNIDIS,1997).

Sintomas oculares podem desenvolver-se após transplante da medula óssea, tanto pela doença enxerto *versus* hospedeiro como pela radioterapia de corpo inteiro, que integra protocolos de condicionamento que antecedem o transplante de medula óssea. Melhorias recentes no manejo geral desses pacientes têm resultado no reconhecimento mais frequente dos problemas oculares. MO da síndrome enxerto *versus* hospedeiro incluem ceratoconjuntivite sicca, lagoftalmo cicatricial, conjuntivite por pseudomonas ou estéril, defeitos epiteliais, úlcera corneana, uveíte e ectrópio da pálpebra (CLAES, 2000: KASMANN, 1993).

Nos últimos anos foram introduzidas muitas novas drogas anticancerosas, tanto na prática clínica quanto como parte de protocolos de pesquisa. Para muitos destes, a ampla gama de efeitos colaterais ainda não é conhecida. Bussulfan, por exemplo, foi identificado

como causa de catarata subcapsular posterior (RAVINDRANATHAN, 1972). Vincristina e vinblastina são tóxicos ao sistema nervoso e afetam principalmente os nervos periféricos, podendo acometer os motores ocular e do trigêmeo. Vincristina também foi apontada como causa de atrofia óptica (SHURIN, 1982).

Os GC, por sua vez, usados em dose imunossupressora durante a fase de indução e manutenção, aumentam significativamente o risco de o paciente desenvolver catarata subcapsular posterior, seu principal efeito colateral. Segundo estudo, esse risco é cinco vezes maior quando comparados os pacientes curados com seus irmãos sadios (ESSIG et al., 2014). Outro efeito importante é a Hipertensão Ocular (HO) e glaucoma iatrogênico pelo uso de GC, o glaucoma cortisônico (RAZEGHINEJAD&KATZ, 2012; KERSEY&BROADWAY, 2005; MENDONCA et al., 2014).

2.1.3 Glaucoma Cortisônico e Hipertensão Ocular

A descoberta dos GC foi um grande avanço no tratamento de várias doenças. À semelhança de outros agentes terapêuticos, têm seus próprios efeitos colaterais, incluindo HO e glaucoma iatrogênico (RAZEGHINEJAD; KATZ, 2012).

O glaucoma é a principal causa de cegueira irreversível, mas previnível, do mundo. Tem como principal causa o aumento da Pressão Intra Ocular (PIO) (POMORSKA et al., 2012), que é mais frequentemente aferida pela técnica de tonometria de aplanação após instilação de anestesia local (proparacaina a 0,5%) e corante de fluoresceína (GOLDMAN, 1957).

A incidência de glaucoma na infância é de 2,29/100 000 pessoas com idade inferior a 20 anos. O glaucoma infantil é uma patologia pediátrica incomum, associada a significante perda visual. Consiste de um grupo heterogêneo de doenças que geram neuropatia óptica e perda de campo visual, e que pode ser classificado em primário, secundário e adquirido (APONTE; DIEHL; MOHNEY, 2010) .

Glaucoma primário é geralmente dividido em congênito (cujo início se dá desde o nascimento até o final do período de recém-nascido) e primário juvenil de ângulo aberto (cujo início se dá mais frequentemente dos quatro anos até o período de adulto jovem). O glaucoma primário congênito é o principal tipo observado na infância (APONTE; DIEHL; MOHNEY, 2010). Ainda no grupo dos glaucomas congênitos, os secundários associam-se a alterações sindrômicas ou a outras condições presentes ao nascimento, como aniridia, sídrome de

Axenfeld-Rieger, retinopatia da prematuridade, síndrome de Rubinstein-Taybi, síndrome de Sturge-Weber, persistência do vítreo hiperplástico primário e rubéola congênita (APONTE; DIEHL; MOHNEY, 2010). Glaucoma adquirido é resultado de outros processos não presentes ao nascimento como inflamação, drogas (como GC), trauma e cirurgia (APONTE; DIEHL; MOHNEY, 2010).

HO induzida por GC foi primeiramente descrita em 1950 com a observação de glaucoma em associação com a administração de GC sistêmico. (MCLEAN,1950). As rotas mais comuns de indução HO são a administração tópica, intra-ocular ou periocular. Pode também ocorrer depois de uso sistêmico, aplicação na pele , intranasal, ou por inalação (URBAN; DREYER, 1993). Estudo prévio mostrou possibilidade de HO em valores elevados, em criança com Síndrome Nefrótica, usuária de GC (BRITO; SILVA; COTTA, 2012). Geralmente ocorre com algumas semanas de uso de GC em paciente suceptíveis, mas é geralmente reversível com a descontinuação do tratamento. Entretanto, se o tratamento for prolongado, pode resultar em neuropatia óptica (NG, PAK C. et al, 2008; SPAETH; DE BARROS; FUDEMBERG, 2009; Q ASHTON ACTON, 2011). As alterações glaucomatológicas comprometem não somente o nervo óptico como também interferem nos mecanismos que causam elevação da PIO, como aumentando a resistência à drenagem do humor aquoso pela malha trabecular (TM) (CLARK; WORDINGER, 2009; DANIAS et al., 2011). Além disso, o aumento da PIO pode ser pela própria infiltração da leucemia na malha trabecular (ROWAN, 1976).

Assim, o uso de GC podem acarretar HO e gerar uma patologia semelhante ao Glaucoma Crônico de Ângulo Aberto (POAG) (SCHWARTZ et al., 2002). Estudos em pacientes tratados com potentes GC tópicos ou sistêmicos mostraram o desenvolvimento de HO em 30 a 40% dos casos, pela diminuição da drenagem do humor aquoso associada a modificações morfológicas na TM (ARMALY; BECKER, 1965) devido ao maior acúmulo de proteínas como a fibronectina e miocilina além da degradação do ativador do plasminogênio tecidual (TPA), e/ou matriz de metaloproteinase-2 (MMP_2) responsáveis pela homeostasia do sistema de drenagem do humor aquoso na câmara anterior, TM e consequentemente aumento da PIO (STAMER et al., 2013). Em adição, foi observado que pacientes mais sensíveis ao uso de GC possuem susceptibilidade maior para desenvolver POAG. Esses pacientes apresentam nível elevado de cortisol sérico e metabolismo anormal de cortisol ocular (CLARK et al., 1995).

A administração de GC pode aumentar a PIO em 90% dos pacientes com POAG. Avaliando-se as pessoas normotensas oculares na população geral, a probabilidade de

aumento da PIO com uso de GC é de 30-40%, caracterizando os médios-responsivos. PIO acima de 31 mm Hg ou 15 mm Hg acima do valor de base ocorre entre 4-6% dos casos, para os altos-responsivos (ZHANG; CLARK; YORIO, 2005). Até 5% dos pacientes não respondem ao tratamento medicamentoso e necessitam cirurgia (RAZEGHINEJAD; KATZ, 2012) .

Embora o glaucoma seja também observado em síndrome de Cushing, desencadeada pela produção de excesso endógeno de GC, a probabilidade de elevação da PIO pela administração de GC por via sistêmica é menor do que por via tópica. Geralmente os grupos de pacientes que estão sendo tratados com GC sistêmicos em longo prazo apresentaram maiores médias e maiores picos de valores de PIO que a população normal (HOVLAND; ELLIS, 1967; LEE, 1958). Um estudo encontrou uma incidência de 10% de glaucoma em pacientes transplantados renais que receberam GC (ADHIKARY; SELLS; BASU, 1982). Há correlação positiva entre a PIO e dose de GC (aumento de 1,4 mmHg na PIO média para cada aumento de 10 mg na dose diária média de prednisona administrada) (TRIPATHI et al., 1992).

Vários relatos de casos clínicos mostram aumento da PIO após o uso de GC em crianças (BRITO et al., 2012; THAM et al., 2004; YAMASHITA et al., 2010). Com a suspensão do tratamento a pressão normalmente retorna a níveis normais. Por outro lado, o uso de GC sistêmicos pode gerar aumento assintomático da PIO, inclusive entre os pacientes pediátricos (NG et al., 2008).

Há sugestões da existência de diferenças genéticas entre os pacientes responsivos e não-responsivos. Alguns autores tentam explicar a susceptibilidade genética por mecanismo monozigótico autossômico: heterozigóticos para os médios-responsivos e os homozigóticos para os altos-responsivos (RAZEGHINEJAD; KATZ, 2011). Diversos mecanismos diferentes podem ser responsáveis para as sensibilidades GC entre os indivíduos, incluindo polimorfismos no gene GR (NR3C1), gene regulador do GC, e as diferenças na expressão do GR. A resposta ao GC é regulada pelos níveis relativos do receptor alfa (GRœ) e do regulador negativo (GRß). Linhagens de células da TM de pacientes glaucomatosos têm uma relação GRß-GRœ menor em comparação com as células TM normais, tornando-os mais sensíveis aos GCs (STAMER et al., 2013). Em situações de homeostase há produção normal de miocilina, fibronectina, glicosaminas e laminas, e degradação na TM do ativador do plasminogênio tecidual (TPA), e/ou matriz de metaloproteinase-2 (MMP_2) mediados pelo GRß-GRœ. Quando há aumento da relação GRœ-GRß ocorre produção aumentada de miocilina e consequentemente menor drenagem de humor aquoso, predispondo ao aumento da

PIO (PFEFFER et al., 2010; STAMER et al., 2013). A diminuição de GRß pode resultar no aumento da resposta ao GC e aumento da PIO (STAMER et al., 2013).

Estudos prévios têm mostrado que alterações morfológicas no nervo óptico e nas camadas de fibras nervosas do nervo óptico podem preceder alterações de campo de visão em pacientes com glaucoma (POMORSKA et al., 2012).

O conhecimento sobre as manifestações oculares da leucemia é importante para o diagnóstico e tratamento da doença, além de muitas vezes refletir o estágio da mesma no organismo. Estudos demonstram que a evidência de envolvimento ocular pode estar associada a pior prognóstico (KINACID, M.C.; GREEN, W.R, 1983; CURTO et al., 1989; KOSHI, K.; TSIARAS, W.G, 1992; REDDY, S.C.; MENON, B.S, 1998).

Poucos estudos foram publicados especificamente relacionando MO em pacientes pediátricos tratados para LLA e nenhum deles foi elaborado de maneira sistemática e prospectiva. A identificação de eventuais complicações oculares de longo prazo decorrentes da própria doença e do tratamento, além de avaliar se as MO possuem correlação com preditores de risco de recidiva da doença e outros fatores (protocolo de tratamento quimioterápico, idade, gênero, óbito, imunofenotipagem e infiltração do CSF por células neoplásicas), poderá subsidiar o delineamento de um protocolo oftalmológico para esses casos.

3. REFERÊNCIAS BIBLIOGRÁFICAS

ADHIKARY, H. P.; SELLS, R. A.; BASU, P. K. Ocular complications of systemic steroid after renal transplantation and their association with HLA. **The British journal of ophthalmology**, v. 66, n. 5, p. 290–291, 1 maio 1982.

ALLEN, R.A.; STRAATSMA, B.R. Ocular involvement in leukaemia and allied disorders. **Arch Ophthalmol** 1961; 66: 490–508.

ALEMAYEHU, W.; SHAMEBO, M.; BEDRI, A.; MENGISTU, Z. Ocular manifestations of leukaemia in Ethiopians. **Ethiop Med J** 1996; 34: 217–224.

ALLEN, R.A.; STRAATSMA, B.R. Ocular involvement in leukaemia and allied disorders. **Arch Ophthalmol** 1961; 66: 490–508.

ALLEMANI, C. et al. Global surveillance of cancer survival 1995–2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2). **The Lancet,** [s.l.], v. 385, n. 9972, p.977-1010, mar. 2015. Elsevier BV. http://dx.doi.org/10.1016/s0140-6736(14)62038-9.

AL-TWEIGERI, T.; NABHOLTZ, J.M.; MACKEY, J.R. Ocular Toxicity and Cancer Chemotherap: A Review. **Cancer,** [s.l.], v. 78, n. 7, p.1359-1373, 1 dez. 1996.

APONTE, E.P.; DIEHL, N.; MOHNEY, B. G. Incidence and clinical characteristics of childhood glaucoma: a population-based study. **Archives of ophthalmology**, v. 128, n. 4, p. 478–482, 2010.

ARIFFIN, H. et al. Young adult survivors of childhood acute lymphoblastic leukemia show evidence of chronic inflammation and cellular aging. **Cancer,** [s.l.], v. 123, n. 21, p.4207-4214, 27 jun. 2017. Wiley-Blackwell. http://dx.doi.org/10.1002/cncr.30857.

ARMALY, M. F.; BECKER, B. Intraocular pressure response to topical corticosteroids. **Federation proceedings**, v. 24, n. 6, p. 1274–1278, 1 nov. 1965.

BALLANTYNE, A.J.; MICHAELSON, I.C. **Textbook of the Fundus of the Eye**. Williams and Wilkins: Baltimore, 1970; 290–292.

BERBIS, J. et al. Cohort Profile: The French Childhood Cancer Survivor Study For Leukaemia (LEA Cohort). **International Journal Of Epidemiology,** [s.l.], v. 44, n. 1, p.49-57, 17 mar. 2014. Oxford University Press (OUP). http://dx.doi.org/10.1093/ije/dyu031.

BRANDALISE, S. R. et al. Benefits of the intermittent use of 6-mercaptopurine and methotrexate in maintenance treatment for low-risk acute lymphoblastic leukemia in children: randomized trial from the Brazilian Childhood Cooperative Group--protocol ALL-99. **Journal of Clinical Oncology**, v. 28, n. 11, p. 1911–1918, 10 abr. 2010.

BRITO, P. et al. Severe ocular hypertension secondary to systemic corticosteroid treatment in a child with nephrotic syndrome. **Clinical Ophthalmology,** [s.l.], p.1675-1679, out. 2012. Dove Medical Press Ltd.. http://dx.doi.org/10.2147/opth.s36261.

ÇAÇA, I. et al. Unilateral Optic Disc Edema in a Patient With Acute Lymphocytic Leukemia: A Case and Review of the Literature. **Annals Of Ophthalmology,** [s.l.], v. 37, n. 4, p.303-306, 2005. Springer Nature. http://dx.doi.org/10.1385/ao:37:4:303.

CAUGHEY RW, MICHELS KB. Birth weight and childhood leukemia: a meta-analysis and review of the current evidence. **Int J Cancer**. 2009;124:2658-2670.

CAVDAR, A.O.; GOZDASOGLU, S.; ARCASOY, A.; DEMIRAG, B. Chloroma-like ocular manifestations in Turkish children with acute myelo-monocytic leukaemia. **Lancet** 1971; 1: 680–682.

CERDÀ-IBÁÑEZ M, BAYO-CALDUCH P, MANFREDA-DOMÍNGUEZ L, DUCH-SAMPER A. Acute Vision Loss As The Only Sign Of Leukemia Relapse. ***Retinal Cases & Brief Reports*** 2018; **12**: 10–11.

CHARIF, C. M.; BELMEKKI, M.; HAJJI, Z.; et al. Ophthalmic manifestations of acute leukemia. **J Fr Ophtal**- mol 2002; 25: 1: 62-6

CHAUDHURI, T.; ROY S.; ROY, PARAG. Ischaemic optic neuropathy induced sudden blindness as an initial presentation of acute lymphoblastic leukemia. **Indian Journal Of Medical And Paediatric Oncology,** [s.l.], v. 34, n. 4, p.335-335, 2013. Medknow. http://dx.doi.org/10.4103/0971-5851.125266.

COGLIANO VJ, BAAN R, STRAIF K, et al. Preventable exposures associated with human cancers. **J Natl Cancer Inst**. 2011; 103:1827-1839.

CLAES, K.; KESTELYN, P. Ocular manifestations of graft versus host disease following bone marrow transplantation. **Bull Soc Belge Ophtalmol** 2000; 77: 21–26.

CLARK, A.F.; WORDINGER, RJ.. The role of steroids in outflow resistance. **Experimental Eye Research,** [s.l.], v. 88, n. 4, p.752-759, abr. 2009. Elsevier BV. http://dx.doi.org/10.1016/j.exer.2008.10.004

COGAN, D.G. Immunosuppression and eye disease. **Am J Ophthalmol** 1977; 83: 777–788.

COLOMBINI, A.; BARZAGHI, A.; CASTAGNETO, M.; BOVO, G.; ROSSI, M.R.; ROVELLI, A.; et al. Retro-orbital late relapse in a child with leukaemia after allogeneic bone marrow transplantation. **Acta Haematol** 1995; 94: 44–47.

CULLIS, C.M.; HINES, D.R.; BULLOCK, J.D. Anterior segment ischaemia: classification and description in chronic myeloid leukaemia. **Ann Ophthalmol** 1979; 11: 1739–1744.

CURTO, M.L.O.; ZINGONE, A.; AQUAVIVA, A.; BAGNULO, S.; CALCULLI, L.; CRISTIANI, L. et al. Leukaemic infiltration of the eye: results of therapy in a retrospective multicentric study. **Med Pediatr Oncol** 1989; 17: 134–139.

DANIAS, J. et al. Gene Expression Changes in Steroid-Induced IOP Elevation in Bovine Trabecular Meshwork. **Investigative Opthalmology & Visual Science,** [s.l.], v. 52, n. 12, p.8636-8645, 7 nov. 2011. Association for Research in Vision and Ophthalmology (ARVO). http://dx.doi.org/10.1167/iovs.11-7563.

DAWSON, D.M.; ROSENTHAL, D.S.; MOLONEY, W.C. Neurologic complications of acute leukaemia in adults: changing rates. **Ann Int Med** 1973; 79: 541–544.

DE CAMARGO B., DE OLIVEIRA S.M, REBELO MS, et al. Cancer incidenceamong children and adolescents in Brazil: first report of 14 population-based cancer registries. **Int J Cancer**. 2010;126:715–720.

DUKE-ELDER, S. System of ophthalmology. **Cornea and conjunctiva**, Vol V111. CV Mosby: St Louis, 1965; 1190–1195.

ESSIG, S. et al. Risk of late effects of treatment in children newly diagnosed with standard-risk acute lymphoblastic leukaemia: a report from the Childhood Cancer Survivor Study cohort. **The Lancet Oncology,** [s.l.], v. 15, n. 8, p.841-851, jul. 2014. Elsevier BV. http://dx.doi.org/10.1016/s1470-2045(14)70265-7.

FRAUNFELDER, F. T.; MEYER, S. MARTHA. Ocular Toxicity of Antineoplastic Agents. **Ophthalmology,** [s.l.], v. 90, n. 1, p.1-3, jan. 1983.

GIAGOUNIDIS, A.A.; MECKENSTOCK, G.; FLACKE, S.; BURK, M.; HOVLAND, K. R.; ELLIS, P. P. Ocular changes in renal transplant patients. **American journal of ophthalmology,** v. 63, n. 2, p. 283–289, 1 fev. 1967.

GOLDMANN H, SCHMIDT T. Über Applanations tonometrie. ***Oph- thalmologica***. 1957;134:221-242.

GORDON, D.M. et al. The Use of Acth and Cortisone in Ophthalmology*. **American Journal Of Ophthalmology,** [s.l.], v. 34, n. 12, p.1675-1686, dez. 1951. Elsevier BV. http://dx.doi.org/10.1016/0002-9394(51)90032-3.

GORDON, K.B. et al. Ocular manifestations of leukemia: leukemic infiltration versus infectious process. **Ophthalmology,** [s.l.], p.2293-2300, dez. 2001.

HONG, S.S. et al. Late Effects, Social Adjustment, and Quality of Life in Adolescent Survivors of Childhood Leukemia. **Journal Of Korean Academy Of Nursing,** [s.l.], v. 44, n. 1, p.55-63, 2014. Korean Society of Nursing Science (KAMJE). http://dx.doi.org/10.4040/jkan.2014.44.1.55.

HOWARD, SC et al. Childhood Cancer Epidemiology in Low-Income Countries. **Cancer** 2008 Feb 1;112(3):461-72. Review.

HYMAN, C.B.; BOGLE, J.M.; BRUBAKER, C.A.; WILLIAMS, K.; HAMMOND, D. Central nervous system involvement by leukaemia in children. **Blood** 1965; 25: 1–12.

KASMANN, B.; RUPRECHT, K.W. Ophthalmologic findings in graft versus host disease (GvHD). **Klin Monatsbl Augenheilkd** 1993; 202: 491–499.

KERSEY, J P; BROADWAY, D C. Corticosteroid-induced glaucoma: a review of the literature. **Eye,** [s.l.], v. 20, n. 4, p.407-416, 6 maio 2005. Springer Nature. http://dx.doi.org/10.1038/sj.eye.6701895.

KINCAID, M. C.; GREEN, W.richard. Ocular and orbital involvement in leukemia. **Survey Of Ophthalmology,** [s.l.], v. 27, n. 4, p.211-232, jan. 1983. Elsevier BV. http://dx.doi.org/10.1016/0039-6257(83)90123-6.

KUWABARA, T.; AIELLO, L. Leukaemic military nodule in retina. **Arch Ophthalmol** 1964; 72: 494–497.

JABS, D.A.; HIRST, L.W.; GREEN, W.R.; TUTSCHKA, P.J.; SANTOS, G.W.; BESCHORNER, W.E. The eye in bone marrow transplantation. II. **Histopathology. Arch Ophthalmol** 1983; 101: 585–590.

JAKOBIEC, F.A.; JONES, I.S. Lymphomatous plasmacytic, histiocytic, haematopoietic tumours. In: Jones IS, Jakobiec FA (eds). **Diseases of the Orbit**. Hagerstown Md, Harper and Row, 1979, pp 309 (see pp 345-348).

LEE, P.F. The Influence of Systemic Steroid Therapy on the Intraocular Pressure*. **American Journal Of Ophthalmology,** [s.l.], v. 46, n. 3, p.328-331, set. 1958. Elsevier BV. http://dx.doi.org/10.1016/0002-9394(58)90256-3

LIN, H.F.; DAI, M.S.; KAO, W.Y.; CHAO, T.Y.Unilateral Optic Nerve Leukaemic Infiltration with Sudden Vision Loss Heralding a Systemic Relapse of Acute Lymphoblastic Leukemia. **J Med Sci**;25(2):097-100.

LINET MS, BROWN LM, MBULAITEYE SM, et al. International long-term trends and recent patterns in the incidence of leukemias and lymphomas among children and adolescents ages 0–19 years. **Int J Cancer.**2015;138:1872–1874

LINS, M.M. et al. Incidence and survival of childhood leukemia in Recife, Brazil: A population-based analysis. **Pediatric Blood & Cancer,** [s.l.], v. 64, n. 8, p.1-6, 21 dez. 2016. Wiley-Blackwell. http://dx.doi.org/10.1002/pbc.26391.

MARCOUX, S. et al. The PETALE study: Late adverse effects and biomarkers in childhood acute lymphoblastic leukemia survivors. **Pediatric Blood & Cancer,** [s.l.], v. 64, n. 6, p.1-8, 4 dez. 2016. Wiley-Blackwell. http://dx.doi.org/10.1002/pbc.26361.

MARGOLIN J, RABIN KR, STEUBER CP, POPLACK, DG. Acute lymphoblastic leukemia. In:Pizzo PA, Poplack DG, eds. **Principles and Practice of Pediatric Oncology.** 6th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010:518-565.

MCLEAN, J.M. Use of ACTH and cortisone. **Trans Am Ophthamol Soc**,vol.48, p. 293-296, 1950

MENDONCA, C. Q. et al. Steroid-induced ocular hypertensive response in children and adolescents with acute lymphoblastic leukemia and non-hodgkin lymphoma. **Pediatric Blood & Cancer,** [s.l.], v. 61, n. 11, p.2083-2085, 17 ago. 2014. Wiley-Blackwell. http://dx.doi.org/10.1002/pbc.25070

MEREDITH, T.A.; AABERG, T.M.; REESER, F.H. Rhegmatogenous retinal detachment complicating CMV retinitis. **Am J Ophthalmol** 1979; 87: 793–796.

MERTENS, ANN C. et al. Health and well-being in adolescent survivors of early childhood cancer: a report from the Childhood Cancer Survivor Study. **Psycho-oncology,** [s.l.], v. 23, n. 3, p.266-275, 4 out. 2013. Wiley-Blackwell. http://dx.doi.org/10.1002/pon.3414.

MORENO F, LORIA D, ABRIATA G, TERRACINI B. Childhood cancer: incidence and early deaths in Argentina, 2000–2008. **Eur J Cancer**. 2013;49:465–473.

NG, PAK C. et al. Transient Increase in Intraocular Pressure during a Dose-Tapering Regime of Systemic Dexamethasone in Preterm Infants. **Ophthalmology,** [s.l.], v. 115, n. 5, p.7-14, maio 2008. Elsevier BV. http://dx.doi.org/10.1016/j.ophtha.2008.01.010

NGUYEN, H.S.; HAIDER, K.M.; ACKERMAN, L.L.Unusual causes of papilledema: Two illustrative cases. **Surg Neurol Int**;4):60, 2013.

OHKOSHI, K.; TSIARAS, W.G. Prognostic importance of ophthalmic manifestations in childhood leukaemia. **Br J Ophthalmol** 1992; 76: 651–655.

PERRY, H.D.; MALLEN, F.J. Iris involvement in granulocytic sarcoma. **Am J Ophthalmol** 1979; 87: 530–532.

PFEFFER, B.A. et al. Reduced Myocilin Expression in Cultured Monkey Trabecular Meshwork Cells Induced by a Selective Glucocorticoid Receptor Agonist: Comparison with Steroids. **Investigative Opthalmology & Visual Science,** [s.l.], v. 51, n. 1, p.437-446, 1 jan. 2010. Association for Research in Vision and Ophthalmology (ARVO). http://dx.doi.org/10.1167/iovs.09-4202.

POMORSKA, M. et al. Application of optical coherence tomography in glaucoma suspect eyes. **Clinical And Experimental Optometry,** [s.l.], v. 95, n. 1, p.78-88, 10 out. 2011. Wiley-Blackwell. http://dx.doi.org/10.1111/j.1444-0938.2011.00654.x.

PRAKASH, A. et al. Ocular manifestations in leukemia and myeloproliferative disorders and their association with hematological parameters. **Annals Of African Medicine,** [s.l.], v. 15, n. 3, p.97-97, 2016. Medknow. http://dx.doi.org/10.4103/1596-3519.188887

QASHTON, A.P. Advances in Ocular Hypertension Research and Treatment: 2011 Edition, **Scholarly Brief**, Atlanta,Georgia: Edition, ScholarlyBrief. p68-69,2011.

RAVINDRANATHAN, M.P.; PAUL, V.J.; KURIAKOSE, E.T. Cataract after busulphan treatment. **Br Med J** 1972; 1: 218–219.

RAZEGHINEJAD, M. REZA; KATZ, L. JAY. Steroid-Induced Iatrogenic Glaucoma. **Ophthalmic Research,** [s.l.], v. 47, n. 2, p.66-80, 2012. S. Karger AG. http://dx.doi.org/10.1159/000328630

REESE, A.B.; GUY, L. Exophthalmos in leukaemia. **Am J Ophthalmol** 1933; 16: 718–720.

REDDY, S. C.; MENON, B. S.. A prospective study of ocular manifestations in childhood acute leukaemia. **Acta Ophthalmologica Scandinavica,** [s.l.], v. 76, n. 6, p.700-703, dez. 1998. Wiley-Blackwell. http://dx.doi.org/10.1034/j.1600-0420.1998.760614.x

RIDGWAY, E.W.; JAFFE, N.; WALTON, D.S. Leukemic ophthalmopathy in children. **Cancer** 1976; 38: 1744–1746.

ROMAN, E et al., Childhood acute lymphoblastic leukaemiaand birthweight: insights from a pooled analysis of case-control data from Germany, the United Kingdom and the United States. **Eur J Cancer**. 2013;49:1437-1447.

ROWAN, P.J.; SLOAN, J.B. Iris and Anterior chamber involvement in leukaemia. **Ann Ophthalmol** 1976; 8: 1081–1085.

SHARMA, T et al. Ophthalmic manifestations of acute leukaemias: the ophthalmologist's role. **Eye,** [s.l.], v. 18, n. 7, p.663-672, 27 fev. 2004. Springer Nature. http://dx.doi.org/10.1038/sj.eye.6701308.

SCHMID, K.E. et al. Update on Ocular Complications of Systemic Cancer Chemotherapy. **Survey Of Ophthalmology,** [s.l.], v. 51, n. 1, p.19-40, jan. 2006. Elsevier BV. http://dx.doi.org/10.1016/j.survophthal.2005.11.001.

SCHWARTZ, B. et al. Dose Response of Dexamethasone for the Enhanced Ocular Hypotensive Response to Epinephrine in Rabbits With Prior Dexamethasone Treatment. **Journal Of Ocular Pharmacology And Therapeutics,** [s.l.], v. 18, n. 2, p.133-139, abr. 2002. Mary Ann Liebert Inc. http://dx.doi.org/10.1089/108076802317373897

SETH, R.; SINGH, A. Leukemias in Children. **The Indian Journal Of Pediatrics,** [s.l.], v. 82, n. 9, p.817-824, 15 fev. 2015. Springer Nature. http://dx.doi.org/10.1007/s12098-015-1695-5.

SHAW, R.K.; MOORE, E.W.; FREIREICH, E.J.; THOMAS, L.B. Meningeal leukaemia. **Neurology** 1960; 10: 823–833.

SHUYUAN L.; MING Z.; YUNXIA G.. Acute bilateral retina hemorrhages beneath internal limiting membrane: An unusual ophthalmological case report of acute leukemia during complete clinical remission. Medicine. 97(7):e0000, FEB 2018,DOI: 10.1097/MD.0000000000010000, PMID: 29443727,Issn Print: 0025-7974,Publication Date: 2018/02/01.

SHIBATA, K.; SHIMAMOTO, Y.; NISHIMURA, T.; OKINAMI, S.; YAMADA, H.; MIYAHARA, M. Ocular manifestation in adult T cell leukaemia/lymphoma. **Ann Hematol** 1997; 74: 163–168.

SHURIN, S.B.; REKATE, H.L.; ANNABLE, W. Optic atrophy induced by vincristine. **Pediatrics** 1982; 70: 288–291.

SOYLU, M.; OZDEMIR, G.; ANLI, A. Pediatric uveitis in southern Turkey. **Ocul Immunol Inflamm** 1997; 5: 197–202.

SPAETH, G.L.; BARROS, DS.M.; FUDEMBERG, S.J.. Visual Loss Caused by Corticosteroid-Induced Glaucoma: How to Avoid It. **Retina,** [s.l.], v. 29, n. 8, p.1057-1061, set. 2009. Ovid Technologies (Wolters Kluwer Health). http://dx.doi.org/10.1097/iae.0b013e3181b32cfd.

STAMER, W. D. et al. Unique Response Profile of Trabecular Meshwork Cells to the Novel Selective Glucocorticoid Receptor Agonist, GW870086X. **Investigative Opthalmology & Visual Science,** [s.l.], v. 54, n. 3, p.2100-2107, 27 mar. 2013. Association for Research in Vision and Ophthalmology (ARVO). http://dx.doi.org/10.1167/iovs.12-11298

TALCOTT, K.E.; GARG, R.J.; GARG, S.J.. Ophthalmic manifestations of leukemia. **Current Opinion In Ophthalmology,** [s.l.], v. 27, n. 6, p.545-551, nov. 2016. Ovid Technologies (Wolters Kluwer Health). http://dx.doi.org/10.1097/icu.0000000000000309

TERWILLIGER, T; ABDUL-HAY, M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. **Blood Cancer Journal,** [s.l.], v. 7, n. 6, p.577-577, 30 jun. 2017. Springer Nature. http://dx.doi.org/10.1038/bcj.2017.53.

THAM, C.C.Y. et al. Intraocular pressure profile of a child on a systemic corticosteroid. **American Journal Of Ophthalmology,** [s.l.], v. 137, n. 1, p.198-201, jan. 2004. Elsevier BV. http://dx.doi.org/10.1016/s0002-9394(03)00838-9.

TRAMA, A et al. Survival of European adolescents and young adults diagnosed with cancer in 2000–07: population-based data from EUROCARE-5. **The Lancet Oncology**, [s.l.], v. 17, n. 7, p.896-906, jul. 2016. Elsevier BV. http://dx.doi.org/10.1016/s1470-2045(16)00162-5.

TRIPATHI, R. C. et al. Corticosteroid treatment for inflammatory bowel disease in pediatric patients increases intraocular pressure. **Gastroenterology**, v. 102, n. 6, p. 1957–1961, 1992.

URBAN, R. C.; DREYER, E. B. Corticosteroid-induced glaucoma. **International Ophthalmology Clinics**, v. 33, n. 2, p. 135–139, 1993.

VIANA S, DE LIMA L, DO NASCIMENTO J, CARDOSO C, ROSÁRIO A, MENDONÇA C et al. Secular trends and predictors of mortality in acute lymphoblastic leukemia for children of low socioeconomic level in Northeast Brazil. Leukemia Research. 2015;39(10):1060-1065.

WALTON, R.C.; REED, K.L. Herpes zoster ophthalmicus following bone marrow transplantation in children. **Bone Marrow Transplant** 1999; 23: 1317–1320.

WARD, E. et al. Childhood and adolescent cancer statistics, 2014. **Ca: A Cancer Journal for Clinicians**, [s.l.], v. 64, n. 2, p.83-103, 31 jan. 2014. American Cancer Society. http://dx.doi.org/10.3322/caac.21219.

WATANABE,A. Recent advance in treatmentof childhood acute lymphoblastic leukemia. **Gan to Kagaku Ryoho**, v.34, p.150-155, 2007

WEHMEIER, A.; AUL, C. et al. Pseudamonas aeruginosa blepharoconjunctivitis during cytoreductive chemotherapy in a woman with acute lymphocytic leukaemia. **Ann Hematol** 1997; 75: 121–123

WHELAN, K. F. et al. Ocular late effects in childhood and adolescent cancer survivors: A report from the childhood cancer survivor study**. Pediatric Blood & Cancer**, [s.l.], v. 54, n. 1, p.103-109, jan. 2010. Wiley-Blackwell. http://dx.doi.org/10.1002/pbc.22277.

YALCINBAYIR, O. et al. Spectral domain optical coherence tomography findings of patients under treatment for pediatric acute lymphoblastic leukemia. **Journal Of American Association For Pediatric Ophthalmology And Strabismus**, [s.l.], v. 21, n. 2, p.131-135, abr. 2017. Elsevier BV. http://dx.doi.org/10.1016/j.jaapos.2016.12.002.

YAMASHITA, T. et al. Steroid-induced Glaucoma in Children With Acute Lymphoblastic Leukemia. **Journal Of Glaucoma,** [s.l.], v. 19, n. 3, p.188-190, mar. 2010. Ovid Technologies (Wolters Kluwer Health). http://dx.doi.org/10.1097/ijg.0b013e3181af321d

YASMEEN, N.; ASHRAF, S. Childhood acute lymphoblastic leukaemia; epidemiology and clinicopathological features. **JPMA:The Journal of the Pakistan Medical Association**, v. 59, n. 3, p. 150–153, 2009.

YEOH, A. E. J et al. Management of adult and paediatric acute lymphoblastic leukaemia in Asia: resource-stratified guidelines from the Asian Oncology Summit 2013. **The Lancet Oncology,** [s.l.], v. 14, n. 12, p.508-523, nov. 2013. Elsevier BV. http://dx.doi.org/10.1016/s1470-2045(13)70452-2.

YOUNG, J. L. et al. Cancer incidence, survival, and mortality for children younger than age 15 years. **Cancer**, v. 58, n. 2, p. 598-602, 1986

ZHANG, X; CLARK, A. F.; YORIO, T.. Regulation of Glucocorticoid Responsiveness in Glaucomatous Trabecular Meshwork Cells by Glucocorticoid Receptor-β. **Investigative Opthalmology & Visual Science,** [s.l.], v. 46, n. 12, p.62-66, 1 dez. 2005. Association for Research in Vision and Ophthalmology (ARVO). http://dx.doi.org/10.1167/iovs.05-0571.

4. REGRAS PARA PUBLICAÇÃO

LEUKEMIA RESEARCH

AUTHOR INFORMATION PACK

TABLE OF CONTENTS

• **Description**
• **Audience**
• **Impact Factor**
• **Abstracting and Indexing**
• **Editorial Board**
• **Guide for Authors**

DESCRIPTION

Leukemia Research an international journal which brings **comprehensive** and **current** information to all health care professionals involved in basic and applied clinical research in **hematological malignancies**. The editors encourage the submission of articles relevant to hematological malignancies. The Journal scope includes reporting studies of **cellular** and **molecular biology**, **genetics**, **immunology**, **epidemiology**, **clinical evaluation**, and **therapy** of these diseases.

Benefits to authors
We also provide many author benefits, such as free PDFs, a liberal copyright policy, special discounts on Elsevier publications and much more. Please click here for more information on our author services. Please see our Guide for Authors for information on article submission. If you require any further information or help, please visit our Support Center

AUDIENCE

Medical scientists, haematologists, immunologists, oncologists and chemotherapists.

IMPACT FACTOR

2017: 2.319 © Clarivate Analytics Journal Citation Reports 2018

ABSTRACTING AND INDEXING

Chemical Abstracts
Current Contents
EMBASE
MEDLINE®
Elsevier BIOBASE
Sociedad Iberoamericana de Informacion Cientifica (SIIC) Data Bases

PASCAL/CNRS
Scopus
Science Citation Index
BIOSIS
AUTHOR INFORMATION PACK 2 Feb 2019 www.elsevier.com/locate/leukres 2

EDITORIAL BOARD

J. Johnston, Winnipeg, Manitoba, Canada
D. Kaplan, Cleveland, Ohio, USA
M. Kashimura, Matsudo, Chiba, Japan
M-C, Kyrtsonis, Athens, Greece
J. Liesveld, Rochester, New York, USA
B. Medeiros, Stanford, California, USA
P. Minetto, Genova, Italy
M. Mraz, Brno, Czech Republic
P. Musto, Rionero in Vulture (Pz), Italy
A. Oyekunle, Gabarone, Botswana
S. A. Parikh, Rochester, Minnesota, USA
J.E. Pimanda, Sydney, New South Wales, Australia
L.F. Porrata, Rochester, Minnesota, USA
S. Rangarajan, Birmingham, Alabama, USA
F. Rassool, Baltimore, Maryland, USA
A. Rawstron, Leeds, England, UK
J. Scandura, New York, USA
S. A. Schichman, Little Rock, Arkansas, Arkansas, USA
K. Seiter, New York, USA
R. P. Taylor, Charlottesville, Virginia, USA
M. Topp, Würzburg, Germany
P. Valent, Vienna, Austria
J. Wang, China
AUTHOR INFORMATION PACK 2 Feb 2019 www.elsevier.com/locate/leukres 3
J.J.L. Wong, Camperdown, New South Wales, Australia
S. Yeh, Taichung, Taiwan
A.S.M. Yong, Adelaide, South Australia, Australia
Q. Zhang, Tianjin, China
AUTHOR INFORMATION PACK 2 Feb 2019 www.elsevier.com/locate/leukres 4

GUIDE FOR AUTHORS

.

Your Paper Your Way

We now differentiate between the requirements for new and revised submissions. You may choose to submit your manuscript as a single Word or PDF file to be used in the refereeing process. Only when your paper is at the revision stage, will you be requested to put your paper in to a 'correct format' for acceptance and provide the items required for the publication of your article. **To find out more, please visit the Preparation section below.**

INTRODUCTION

Leukemia Research an international journal which brings comprehensive and current information to all health care professionals involved in basic and applied clinical research in hematological malignancies. The editors encourage the submission of articles relevant to hematological malignancies. The Journal scope includes reporting studies of cellular and molecular biology, genetics, immunology, epidemiology, clinical evaluation, and therapy of these diseases.

Word count limit does not include the abstract references, acknowledgement document, figures and tables.

Original Articles are full-length research papers which have not been published previously, except in a preliminary form. An Original paper usually does not exceed 4,000 words, it should be divided into sections (Introduction, Materials and Methods, Results and Discussion), 250 word abstract, longer papers may be considered if relevant, limit of 50 references and limit of 6 figures and/or tables.

Review Articles should be submitted after prior consultation with an Editor. This paper should not exceed 5,000 words but longer papers may be considered if relevant, limit of 150 references and no limit for figures and/or tables.

Editorials do not have abstracts and should not exceed 1,000 words, limit of 5 references and optional 1-2 figures and/or tables. Editorials should be submitted after prior consultation with an Editor.

Correspondence, which encompasses preliminary research observations and research letters, as well as conventional Letters to the Editor. No abstract required. 1,500 words (excluding references only) max 2 figures and tables, 20 References.

Commentaries are contributions invited by the Editor which should be concerned with matters of opinion and criticism on contributions published in the journal and other matters of interest to researchers in our field, often invited by the Editor to present new perspectives and advance understanding of controversial issues by provoking debate and comment. (1,500 words, 10 references, 1 figure, 1 table)
Authors may send queries concerning the submission process, manuscript status, or journal procedures to the Editorial Office(e-mail: LR@elsevier.com).

Submission checklist

You can use this list to carry out a final check of your submission before you send it to the journal for review. Please check the relevant section in this Guide for Authors for more details.

Ensure that the following items are present:

One author has been designated as the corresponding author with contact details:
• E-mail address
• Full postal address
All necessary files have been uploaded:
Manuscript:
• Include keywords
• All figures (include relevant captions)
• All tables (including titles, description, footnotes)
• Ensure all figure and table citations in the text match the files provided
• Indicate clearly if color should be used for any figures in print
Graphical Abstracts / Highlights files (where applicable)
Supplemental files (where applicable)

Further considerations
• Manuscript has been 'spell checked' and 'grammar checked'

• All references mentioned in the Reference List are cited in the text, and vice versa
• Permission has been obtained for use of copyrighted material from other sources (including the Internet)
• A competing interests statement is provided, even if the authors have no competing interests to declare
• Journal policies detailed in this guide have been reviewed
• Referee suggestions and contact details provided, based on journal requirements

For further information, visit our Support Center.
The Journal allows up to 6 months for authors to make the suggested revisions to their manuscript.
Note: If you do not submit your revisions by the 6 month date your paper will be withdrawn.

BEFORE YOU BEGIN

Ethics in publishing

Please see our information pages on Ethics in publishing and Ethical guidelines for journal publication.

Studies in humans and animals

If the work involves the use of human subjects, the author should ensure that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The manuscript should be in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals and aim for the inclusion of representative human populations (sex, age and ethnicity) as per those recommendations. The terms sex and gender should be used correctly.

Authors should include a statement in the manuscript that informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects must always be observed.

All animal experiments should comply with the ARRIVE guidelines and should be carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978) and the authors should clearly indicate in the manuscript that such guidelines have been followed. The sex of animals must be indicated, and where appropriate, the influence (or association) of sex on the results of the study.

Declaration of interest

All authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work. Examples of potential competing interests include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding. Authors must disclose any interests in two places: 1. A summary declaration of interest statement in the title page file (if double-blind) or the manuscript file (if single-blind). If there are no interests to declare then please state this: 'Declarations of interest: none'. This summary statement will be ultimately published if the article is accepted. 2. Detailed disclosures as part of a separate Declaration of Interest form, which forms part of the journal's official records. It is important

for potential interests to be declared in both places and that the information matches. More information.

Submission declaration and verification

Submission of an article implies that the work described has not been published previously (except in the form of an abstract, a published lecture or academic thesis, see 'Multiple, redundant or concurrent publication' for more information), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyrightholder.
To verify originality, your article may be checked by the originality detection service Crossref Similarity Check.

Preprints

Please note that preprints can be shared anywhere at any time, in line with Elsevier's sharing policy. Sharing your preprints e.g. on a preprint server will not count as prior publication (see 'Multiple, redundant or concurrent publication' for more information).

Use of inclusive language

Inclusive language acknowledges diversity, conveys respect to all people, is sensitive to differences, and promotes equal opportunities. Articles should make no assumptions about the beliefs or commitments of any reader, should contain nothing which might imply that one individual is superior to another on the grounds of race, sex, culture or any other characteristic, and should use inclusive language throughout. Authors should ensure that writing is free from bias, for instance by using 'he or she', 'his/her' instead of 'he' or 'his', and by making use of job titles that are free of stereotyping (e.g. 'chairperson' instead of 'chairman' and 'flight attendant' instead of 'stewardess').

Authorship

All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Role of Corresponding Author

Please note: there is only one corresponding author of the manuscript. The corresponding author is the one that submits the manuscript and has the duty to ensure that all of the named authors have seen and approved the original manuscript and subsequent revisions. Each author should have participated sufficiently in the work to take public responsibility for the content. The corresponding author should also ensure that those who have contributed to the research are acknowledged appropriately either as a co-author or in the Acknowledgements. In addition, the corresponding author has the prime responsibility for ensuring the paper is correctly prepared according to the Guide for Authors. Submitted manuscripts not complying with the Guide for Authors may be returned to the authors.

Changes to authorship

Authors are expected to consider carefully the list and order of authors **before** submitting their manuscript and provide the definitive list of authors at the time of the original submission. Any addition, deletion or rearrangement of author names in the authorship list should be made only **before** the manuscript has been accepted and only if approved by the journal Editor. To request such a change, the Editor must receive the following from the

corresponding author: (a) the reason for the change in author list and (b) written confirmation (e-mail, letter) from all authors that they agree with the addition, removal or rearrangement. In the case of addition or removal of authors, this includes confirmation from the author being added or removed.
Only in exceptional circumstances will the Editor consider the addition, deletion or rearrangement of authors **after** the manuscript has been accepted. While the Editor considers the request, publication of the manuscript will be suspended. If the manuscript has already been published in an online issue, any requests approved by the Editor will result in a corrigendum.

Clinical trial results

In line with the position of the International Committee of Medical Journal Editors, the journal will not consider results posted in the same clinical trials registry in which primary registration resides to be prior publication if the results posted are presented in the form of a brief structured (less than 500 words) abstract or table. However, divulging results in other circumstances (e.g., investors' meetings) is discouraged and may jeopardise consideration of the manuscript. Authors should fully disclose all posting in registries of results of the same or closely related work.

Reporting clinical trials

Randomized controlled trials should be presented according to the CONSORT guidelines. At manuscript submission, authors must provide the CONSORT checklist accompanied by a flow diagram that illustrates the progress of patients through the trial, including recruitment, enrollment, randomization, withdrawal and completion, and a detailed description of the randomization procedure. The CONSORT checklist and template flow diagram are available online.

Registration of clinical trials

Registration in a public trials registry is a condition for publication of clinical trials in this journal in accordance with International Committee of Medical Journal Editors recommendations. Trials must register at or before the onset of patient enrolment. The clinical trial registration number should be included at the end of the abstract of the article. A clinical trial is defined as any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects of health outcomes. Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example drugs, surgical procedures, devices, behavioural treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) will not require registration.

Article transfer service

This journal is part of our Article Transfer Service. This means that if the Editor feels your article is more suitable in one of our other participating journals, then you may be asked to consider transferring the article to one of those. If you agree, your article will be transferred automatically on your behalf with no need to reformat. Please note that your article will be reviewed again by the new journal.

Copyright

Upon acceptance of an article, authors will be asked to complete a 'Journal Publishing Agreement'. An e-mail will be sent to the corresponding author confirming receipt of the manuscript together with a 'Journal Publishing Agreement' form or a link to the online version of this agreement.

Subscribers may reproduce tables of contents or prepare lists of articles including abstracts for internal circulation within their institutions. Permission of the Publisher is required for resale or distribution outside the institution and for all other derivative works, including compilations and translations. If excerpts from other copyrighted works are included, the author(s) must obtain written permission from the copyright owners and credit the source(s) in the article. Elsevier has preprinted forms for use by authors in these cases.

For gold open access articles: Upon acceptance of an article, authors will be asked to complete na 'Exclusive License Agreement' (more information). Permitted third party reuse of gold open Access articles is determined by the author's choice of user license.

Author rights
As an author you (or your employer or institution) have certain rights to reuse your work.

Elsevier supports responsible sharing
Find out how you can share your research published in Elsevier journals.

Role of the funding source
You are requested to identify who provided financial support for the conduct of the research and/or preparation of the article and to briefly describe the role of the sponsor(s), if any, in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. If the funding source(s) had no such involvement then this should be stated.

Funding body agreements and policies
Elsevier has established a number of agreements with funding bodies which allow authors to comply with their funder's open access policies. Some funding bodies will reimburse the author for the gold open access publication fee. Details of existing agreements are available online.
After acceptance, open access papers will be published under a noncommercial license. For authors requiring a commercial CC BY license, you can apply after your manuscript is accepted for publication.

Open access
This journal offers authors a choice in publishing their research:

Subscription
• Articles are made available to subscribers as well as developing countries and patient groups through our universal access programs.
• No open access publication fee payable by authors.
• The Author is entitled to post the accepted manuscript in their institution's repository and make this public after an embargo period (known as green Open Access). The published journal article cannot be shared publicly, for example on ResearchGate or Academia.edu, to ensure the sustainability of peerreviewed research in journal publications. The embargo period for this journal can be found below.

Gold open access
• Articles are freely available to both subscribers and the wider public with permitted reuse.
• A gold open access publication fee is payable by authors or on their behalf, e.g. by their research funder or institution.

Regardless of how you choose to publish your article, the journal will apply the same peer review criteria and acceptance standards.

For gold open access articles, permitted third party (re)use is defined by the following Creative Commons user licenses:

Creative Commons Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)
For non-commercial purposes, lets others distribute and copy the article, and to include in a collective work (such as an anthology), as long as they credit the author(s) and provided they do not alter or modify the article.
The gold open access publication fee for this journal is **USD 3250**, excluding taxes. Learn more about Elsevier's pricing policy: https://www.elsevier.com/openaccesspricing.

Green open access
Authors can share their research in a variety of different ways and Elsevier has a number of green open access options available. We recommend authors see our open access page for further information. Authors can also self-archive their manuscripts immediately and enable public access from their institution's repository after an embargo period. This is the version that has been accepted for publication and which typically includes author-incorporated changes suggested during submission, peer review and in editor-author communications. Embargo period: For subscription articles, na appropriate amount of time is needed for journals to deliver value to subscribing customers before an article becomes freely available to the public. This is the embargo period and it begins from the date the article is formally published online in its final and fully citable form. Find out more.

This journal has an embargo period of 12 months.

Elsevier Researcher Academy
Researcher Academy is a free e-learning platform designed to support early and mid-career researchers throughout their research journey. The "Learn" environment at Researcher Academy offers several interactive modules, webinars, downloadable guides and resources to guide you through the process of writing for research and going through peer review. Feel free to use these free resources to improve your submission and navigate the publication process with ease.

Language (usage and editing services)
Please write your text in good English (American or British usage is accepted, but not a mixture of these). Authors who feel their English language manuscript may require editing to eliminate possible grammatical or spelling errors and to conform to correct scientific English may wish to use the English Language Editing service available from Elsevier's WebShop.

Informed consent and patient details
Studies on patients or volunteers require ethics committee approval and informed consent, which should be documented in the paper. Appropriate consents, permissions and releases

must be obtained where an author wishes to include case details or other personal information or images of patients and any other individuals in an Elsevier publication. Written consents must be retained by the author but copies should not be provided to the journal. Only if specifically requested by the journal in exceptional circumstances (for example if a legal issue arises) the author must provide copies of the consents or evidence that such consents have been obtained. For more information, please review the Elsevier Policy on the Use of Images or Personal Information of Patients or other Individuals. Unless you have written permission from the patient (or, where applicable, the next of kin), the personal details of any patient included in any part of the article and in any supplementary materials (including all illustrations and videos) must be removed before submission.

Submission

Our online submission system guides you stepwise through the process of entering your article details and uploading your files. The system converts your article files to a single PDF file used in the peer-review process. Editable files (e.g., Word, LaTeX) are required to typeset your article for final publication. All correspondence, including notification of the Editor's decision and requests for revision, is sent by e-mail.

Submit your article

Please submit your article via http://ees.elsevier.com/lr/.

Referees

Please submit the names and institutional e-mail addresses of several potential referees. For more details, visit our Support site. Note that the editor retains the sole right to decide whether or not the suggested reviewers are used.

PREPARATION

NEW SUBMISSIONS

Submission to this journal proceeds totally online and you will be guided stepwise through the creation and uploading of your files. The system automatically converts your files to a single PDF file, which is used in the peer-review process.

As part of the Your Paper Your Way service, you may choose to submit your manuscript as a single file to be used in the refereeing process. This can be a PDF file or a Word document, in any format or layout that can be used by referees to evaluate your manuscript. It should contain high enough quality figures for refereeing. If you prefer to do so, you may still provide all or some of the source files at the initial submission. Please note that individual figure files larger than 10 MB must be uploaded separately.

References

There are no strict requirements on reference formatting at submission. References can be in any style or format as long as the style is consistent. Where applicable, author(s) name(s), journal title/ book title, chapter title/article title, year of publication, volume number/book chapter and the article number or pagination must be present. Use of DOI is highly encouraged. The reference style used by the journal will be applied to the accepted article by Elsevier at the proof stage. Note that missing data will be highlighted at proof stage for the author to correct.

Formatting requirements

There are no strict formatting requirements but all manuscripts must contain the essential elements needed to convey your manuscript, for example Abstract, Keywords, Introduction, Materials and Methods, Results, Conclusions, Artwork and Tables with Captions.
If your article includes any Videos and/or other Supplementary material, this should be included in your initial submission for peer review purposes. Divide the article into clearly defined sections.

Figures and tables embedded in text
Please ensure the figures and the tables included in the single file are placed next to the relevant text in the manuscript, rather than at the bottom or the top of the file. The corresponding caption should be placed directly below the figure or table.

Peer review
This journal operates a single blind review process. All contributions will be initially assessed by the editor for suitability for the journal. Papers deemed suitable are then typically sent to a minimum of two independent expert reviewers to assess the scientific quality of the paper. The Editor is responsible for the final decision regarding acceptance or rejection of articles. The Editor's decision is final. More information on types of peer review.

REVISED SUBMISSIONS
Use of word processing software
Regardless of the file format of the original submission, at revision you must provide us with na editable file of the entire article. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier). See also the section on Electronic artwork.
To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

Article structure
Subdivision - numbered sections
Divide your article into clearly defined and numbered sections. Subsections should be numbered 1.1 (then 1.1.1, 1.1.2, ...), 1.2, etc. (the abstract is not included in section numbering). Use this numbering also for internal cross-referencing: do not just refer to 'the text'. Any subsection may be given a brief heading. Each heading should appear on its own separate line.

Introduction
State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods
Provide sufficient details to allow the work to be reproduced by an independent researcher. Methods that are already published should be summarized, and indicated by a reference. If quoting directly from a previously published method, use quotation marks and also cite the source. Any modifications to existing methods should also be described.

Theory/calculation
A Theory section should extend, not repeat, the background to the article already dealt with in the Introduction and lay the foundation for further work. In contrast, a Calculation section represents a practical development from a theoretical basis.

Results
Results should be clear and concise.

Discussion
This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Conclusions
The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

Appendices
If there is more than one appendix, they should be identified as A, B, etc. Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

Essential title page information

• ***Title.*** Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.
• ***Author names and affiliations.*** Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. You can add your name between parentheses in your own script behind the English transliteration. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lowercase superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
• ***Corresponding author.*** Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. This responsibility includes answering any future queries about Methodology and Materials. **Ensure that the e-mail address is given and that contact details are kept up to date by the corresponding author.**
• ***Present/permanent address.*** If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

Abstract

A concise and factual abstract is required. The abstract should state briefly the purpose of the research, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. For this reason, References should be avoided, but IF essential, then cite the author(s) and year(s). Also, non-standard or uncommon

abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract itself.

The abstract should not exceed 200 words.

Graphical abstract
Although a graphical abstract is optional, its use is encouraged as it draws more attention to the online article. The graphical abstract should summarize the contents of the article in a concise, pictorial form designed to capture the attention of a wide readership. Graphical abstracts should be submitted as a separate file in the online submission system. Image size: Please provide an image with a minimum of 531 × 1328 pixels (h × w) or proportionally more. The image should be readable at a size of 5 ×13 cm using a regular screen resolution of 96 dpi. Preferred file types: TIFF, EPS, PDF or MS Office files. You can view Example Graphical Abstracts on our information site. Authors can make use of Elsevier's Illustration Services to ensure the best presentation of their images and in accordance with all technical requirements.

Highlights
Highlights are mandatory for this journal. They consist of a short collection of bullet points that convey the core findings of the article and should be submitted in a separate editable file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point). You can view example Highlights on our information site.

Keywords
Immediately after the abstract, provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

Abbreviations
Define abbreviations that are not standard in this field in a footnote to be placed on the first Page of the article. Such abbreviations that are unavoidable in the abstract must be defined at their first mention there, as well as in the footnote. Ensure consistency of abbreviations throughout the article.

Acknowledgements
Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

Formatting of funding sources
List funding sources in this standard way to facilitate compliance to funder's requirements:

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

It is not necessary to include detailed descriptions on the program or type of grants and awards. When funding is from a block grant or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding.

If no funding has been provided for the research, please include the following sentence:
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Units
Follow internationally accepted rules and conventions: use the international system of units (SI). If other units are mentioned, please give their equivalent in SI.

Drug names
Use generic names for drugs. Commercial names may be included in parentheses at first mention in the text. Complicated drug names or regimens may be abbreviated, with the abbreviation in parentheses after first mention.

Math formulae
Please submit math equations as editable text and not as images. Present simple formulae in line with normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. In principle, variables are to be presented in italics. Powers of e are often more conveniently denoted by exp. Number consecutively any equations that have to be displayed separately from the text (if referred to explicitly in the text).

Footnotes
Footnotes should be used sparingly. Number them consecutively throughout the article. Many Word processors build footnotes into the text, and this feature may be used. Should this not be the case, indicate the position of footnotes in the text and present the footnotes themselves separately at the end of the article.

Artwork

Electronic artwork
General points
• Make sure you use uniform lettering and sizing of your original artwork.
• Preferred fonts: Arial (or Helvetica), Times New Roman (or Times), Symbol, Courier.
• Number the illustrations according to their sequence in the text.
• Use a logical naming convention for your artwork files.
• Indicate per figure if it is a single, 1.5 or 2-column fitting image.
• For Word submissions only, you may still provide figures and their captions, and tables within a single file at the revision stage.
• Please note that individual figure files larger than 10 MB must be provided in separate source files.
A detailed guide on electronic artwork is available.
You are urged to visit this site; some excerpts from the detailed information are given here.
Formats
Regardless of the application used, when your electronic artwork is finalized, please 'save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):

EPS (or PDF): Vector drawings. Embed the font or save the text as 'graphics'.
TIFF (or JPG): Color or grayscale photographs (halftones): always use a minimum of 300 dpi.
TIFF (or JPG): Bitmapped line drawings: use a minimum of 1000 dpi.
TIFF (or JPG): Combinations bitmapped line/half-tone (color or grayscale): a minimum of 500 dpi is required.
Please do not:
• Supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG); the resolution is too low.
• Supply files that are too low in resolution.
• Submit graphics that are disproportionately large for the content.

Color artwork
Please make sure that artwork files are in an acceptable format (TIFF (or JPEG), EPS (or PDF), or MS Office files) and with the correct resolution. If, together with your accepted article, you submit usable color figures then Elsevier will ensure, at no additional charge, that these figures will appear in color online (e.g., ScienceDirect and other sites) regardless of whether or not these illustrations are reproduced in color in the printed version. **For color reproduction in print, you will receive information regarding the costs from Elsevier after receipt of your accepted article**. Please indicate your preference for color: in print or online only. Further information on the preparation of electronic artwork.

Illustration services
Elsevier's WebShop offers Illustration Services to authors preparing to submit a manuscript but concerned about the quality of the images accompanying their article. Elsevier's expert illustrators can produce scientific, technical and medical-style images, as well as a full range of charts, tables and graphs. Image 'polishing' is also available, where our illustrators take your image(s) and improve them to a professional standard. Please visit the website to find out more.

Figure captions
Ensure that each illustration has a caption. A caption should comprise a brief title (**not** on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.
Please submit tables as editable text and not as images. Tables should be placed next to the relevant text in the article. Number tables consecutively in accordance with their appearance in the text and place any table notes below the table body. Be sparing in the use of tables and ensure that the data presented in them do not duplicate results described elsewhere in the article. Please avoid using vertical rules and shading in table cells.

References

Citation in text
Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been acceptedfor publication and a copy of the title page of the relevant article must be submitted.

Reference links
Increased discoverability of research and high quality peer review are ensured by online links to the sources cited. In order to allow us to create links to abstracting and indexing services, such as Scopus, CrossRef and PubMed, please ensure that data provided in the references are correct. Please note that incorrect surnames, journal/book titles, publication year and pagination may prevent link creation. When copying references, please be careful as they may already contain errors. Use of the DOI is highly encouraged.

A DOI is guaranteed never to change, so you can use it as a permanent link to any electronic article. An example of a citation using DOI for an article not yet in an issue is: VanDecar J.C., Russo R.M., James D.E., Ambeh W.B., Franke M. (2003). Aseismic continuation of the Lesser Antilles slab beneath northeastern Venezuela. Journal of Geophysical Research, https://doi.org/10.1029/2001JB000884. Please note the format of such citations should be in the same style as all other references in the paper.

Web references
As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.),
should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

Data references
This journal encourages you to cite underlying or relevant datasets in your manuscript by citing them in your text and including a data reference in your Reference List. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so we can properly identify it as a data reference. The [dataset] identifier will not appear in your published article.

References in a special issue
Please ensure that the words 'this issue' are added to any references in the list (and any citations in the text) to other articles in the same Special Issue.

Reference management software
Most Elsevier journals have their reference template available in many of the most popular reference management software products. These include all products that support Citation Style Language styles, such as Mendeley. Using citation plug-ins from these products, authors only need to select the appropriate journal template when preparing their article, after which citations and bibliographies will be automatically formatted in the journal's style. If no template is yet available for this journal,
please follow the format of the sample references and citations as shown in this Guide. If you use reference management software, please ensure that you remove all field codes before submitting the electronic manuscript. More information on how to remove field codes from different reference management software.
Users of Mendeley Desktop can easily install the reference style for this journal by clicking the following link:
http://open.mendeley.com/use-citation-style/leukemia-research
When preparing your manuscript, you will then be able to select this style using the Mendeley plugins for Microsoft Word or LibreOffice.

Reference formatting
There are no strict requirements on reference formatting at submission. References can be in any style or format as long as the style is consistent. Where applicable, author(s) name(s), journal title/ book title, chapter title/article title, year of publication, volume number/book chapter and the article number or pagination must be present. Use of DOI is highly encouraged. The reference style used by the journal will be applied to the accepted article by Elsevier at the proof stage. Note that missing data will be highlighted at proof stage for the author to correct. If you do wish to format the references yourself they should be arranged according to the following examples:

Reference style
Text: Indicate references by number(s) in square brackets in line with the text. The actual authors can be referred to, but the reference number(s) must always be given.
Example: '..... as demonstrated [3,6]. Barnaby and Jones [8] obtained a different result ....'
List: Number the references (numbers in square brackets) in the list in the order in which they appear
in the text.
Examples:
Reference to a journal publication:
[1] J. van der Geer, J.A.J. Hanraads, R.A. Lupton, The art of writing a scientific article, J. Sci. Commun. 163 (2010) 51–59. https://doi.org/10.1016/j.Sc.2010.00372.
Reference to a journal publication with an article number:
[2] Van der Geer, J., Hanraads, J.A.J., Lupton, R.A., 2018. The art of writing a scientific article. Heliyon. 19, e00205. https://doi.org/10.1016/j.heliyon.2018.e00205.
Reference to a book:
[3] W. Strunk Jr., E.B. White, The Elements of Style, fourth ed., Longman, New York, 2000.
Reference to a chapter in an edited book:
[4] G.R. Mettam, L.B. Adams, How to prepare an electronic version of your article, in: B.S. Jones, R.Z. Smith (Eds.), Introduction to the Electronic Age, E-Publishing Inc., New York, 2009, pp. 281–304.
Reference to a website:
[5] Cancer Research UK, Cancer statistics reports for the UK. http://www.cancerresearchuk.org/ aboutcancer/statistics/cancerstatsreport/, 2003 (accessed 13 March 2003).
Reference to a dataset:
[dataset] [6] M. Oguro, S. Imahiro, S. Saito, T. Nakashizuka, Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1, 2015. https://doi.org/10.17632/ xwj98nb39r.1.

Journal abbreviations source
Journal names should be abbreviated according to the List of Title Word Abbreviations.

Video
Elsevier accepts video material and animation sequences to support and enhance your scientific research. Authors who have video or animation files that they wish to submit with their article are strongly encouraged to include links to these within the body of the article. This can be done in the same way as a figure or table by referring to the video or animation content and noting in the body text where it should be placed. All submitted files should be

properly labeled so that they directly relate to the video file's content. . In order to ensure that your video or animation material is directly usable, please provide the file in one of our recommended file formats with a preferred maximum size of 150 MB per file, 1 GB in total. Video and animation files supplied will be published online in
the electronic version of your article in Elsevier Web products, including ScienceDirect. Please supply 'stills' with your files: you can choose any frame from the video or animation or make a separate image. These will be used instead of standard icons and will personalize the link to your video data. For more detailed instructions please visit our video instruction pages. Note: since video and animation cannot be embedded in the print version of the journal, please provide text for both the electronic and the print version for the portions of the article that refer to this content.

Data visualization

Include interactive data visualizations in your publication and let your readers interact and engage more closely with your research. Follow the instructions here to find out about available data visualization options and how to include them with your article.

Supplementary material

Supplementary material such as applications, images and sound clips, can be published with your article to enhance it. Submitted supplementary items are published exactly as they are received (Excel or PowerPoint files will appear as such online). Please submit your material together with the article and supply a concise, descriptive caption for each supplementary file. If you wish to make changes to supplementary material during any stage of the process, please make sure to provide an updated file. Do not annotate any corrections on a previous version. Please switch off the 'Track Changes' option in Microsoft Office files as these will appear in the published version.

Research data

This journal encourages and enables you to share data that supports your research publication where appropriate, and enables you to interlink the data with your published articles. Research data refers to the results of observations or experimentation that validate research findings. To facilitate reproducibility and data reuse, this journal also encourages you to share your software, code, models, algorithms, protocols, methods and other useful materials related to the project.
Below are a number of ways in which you can associate data with your article or make a statement about the availability of your data when submitting your manuscript. If you are sharing data in one of these ways, you are encouraged to cite the data in your manuscript and reference list. Please refer to the "References" section for more information about data citation. For more information on depositing, sharing and using research data and other relevant research materials, visit the research data page.

Data linking

If you have made your research data available in a data repository, you can link your article directly to the dataset. Elsevier collaborates with a number of repositories to link articles on ScienceDirect with relevant repositories, giving readers access to underlying data that gives them a better understanding of the research described.
There are different ways to link your datasets to your article. When available, you can directly link your dataset to your article by providing the relevant information in the submission system. For more information, visit the database linking page.

For supported data repositories a repository banner will automatically appear next to your published article on ScienceDirect.
In addition, you can link to relevant data or entities through identifiers within the text of your manuscript, using the following format: Database: xxxx (e.g., TAIR: AT1G01020; CCDC: 734053; PDB: 1XFN).

Mendeley Data
This journal supports Mendeley Data, enabling you to deposit any research data (including raw and processed data, video, code, software, algorithms, protocols, and methods) associated with your manuscript in a free-to-use, open access repository. During the submission process, after uploading your manuscript, you will have the opportunity to upload your relevant datasets directly to *Mendeley Data*. The datasets will be listed and directly accessible to readers next to your published article online.

For more information, visit the Mendeley Data for journals page.

Data statement
To foster transparency, we encourage you to state the availability of your data in your submission. This may be a requirement of your funding body or institution. If your data is unavailable to Access or unsuitable to post, you will have the opportunity to indicate why during the submission process, for example by stating that the research data is confidential. The statement will appear with your published article on ScienceDirect. For more information, visit the Data Statement page.

AFTER ACCEPTANCE

Online proof correction
Corresponding authors will receive an e-mail with a link to our online proofing system, allowing annotation and correction of proofs online. The environment is similar to MS Word: in addition to editing text, you can also comment on figures/tables and answer questions from the Copy Editor. Web-based proofing provides a faster and less error-prone process by allowing you to directly type your corrections, eliminating the potential introduction of errors. If preferred, you can still choose to annotate and upload your edits on the PDF version. All instructions for proofing will be given in the e-mail we send to authors, including alternative methods to the online version and PDF.
We will do everything possible to get your article published quickly and accurately. Please use this proof only for checking the typesetting, editing, completeness and correctness of the text, tables and figures. Significant changes to the article as accepted for publication will only be considered at this stage with permission from the Editor. It is important to ensure that all corrections are sent back to us in one communication. Please check carefully before replying, as inclusion of any subsequent corrections cannot be guaranteed. Proofreading is solely your responsibility.

Offprints
The corresponding author will, at no cost, receive a customized Share Link providing 50 days free access to the final published version of the article on ScienceDirect. The Share Link can be used for sharing the article via any communication channel, including email and social media. For an extra charge, paper offprints can be ordered via the offprint order form which is sent once the article is accepted for publication. Both corresponding and co-authors may order offprints at any time via Elsevier's Webshop. Corresponding authors who have published their article gold open access do not receive a Share Link as their final published version of the

article is available open access on ScienceDirect and can be shared through the article DOI link.

AUTHOR INQUIRIES

Visit the Elsevier Support Center to find the answers you need. Here you will find everything from Frequently Asked Questions to ways to get in touch.

You can also check the status of your submitted article or find out when your accepted article Will be published.