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**APPENDIX** I-V Instructions to authors

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## Steroid resistance in leukemia

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levels and steroid-resistance in patients has been found. In recent years, several other mechanisms of action have been reported that could play an important role in the development of such drug resistances in leukemia.

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### Abstract

There are several types of leukemia which are characterized by the abnormal growth of cells from the myeloid or lymphoid lineage. Because of their lympholytic actions, glucocorticoids (GCs) are included in many therapeutic regimens for the treatment of various forms of leukemia. Although a significant number of acute lymphoblastic leukemia patients respond well to GC treatment during initial phases; prolonged treatments sometimes results in steroid-resistance. The exact mechanism of this resistance has yet not been completely elucidated, but a correlation between functional GC receptor expression levels and steroid-resistance in patients has been found. In recent years, several other mechanisms of action have been reported that could play an important role in the development of such drug resistances in leukemia. Therefore, a better understanding of how leukemic patients develop drug resistance should result in drugs designed appropriately to treat these patients.

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**Key words:** Leukemia; Glucocorticoid; Steroid resistant; Mutations; Genes

**Core tip:** The exact mechanism of this resistance has yet not been completely elucidated, but a correlation between functional glucocorticoid receptor expression

### INTRODUCTION

Leukemia affects a large population of individuals, both young and old; however, those over the age of 60 years are more at risk of developing the disease. Leukemia is characterized by the abnormal growth of cells of the myeloid or lymphoid lineage that can arise due to several factors including chromosomal abnormalities, transcription factor alterations, and/or chromosomal hyperploidy<sup>[1]</sup>. In addition to affecting either the myeloid or lymphoid lineage, leukemia can be classified as either acute or chronic. In acute leukemia, the white blood cells multiply very rapidly and are very immature, and therefore cannot function properly. In chronic leukemia, the blasts form more slowly, allowing the body to continue to producing normal, functional cells. This causes fewer symptoms for the patient but often results in splenomegaly. In all major forms of leukemia, as the leukemic bone marrow cells divide, they crowd the marrow and suppress production and function of other healthy cells. The rate of progression and replacement of normal bone marrow cells with cancerous ones is different with each type of leukemia<sup>[1]</sup>.

### TYPES OF LEUKEMIA

There are four major types of leukemia: chronic lymphoblastic leukemia (CLL), chronic myeloid leukemia (CML), acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL). CLL is mainly caused by unregulated



proliferation of developing B-cells. The lack of growth regulation can be related to the developmental process where B-cells interact with T-cells in the germinal centers of lymph nodes to receive proliferative signaling. In CLL the B-cells express CD19, CD5, and CD23 and have lower levels of IgM, IgD, and CD79b. This phenotype is indicative of an activated mature B-cells<sup>[2]</sup>. CML is a cancer of the hematopoietic stem cell, in which 95% of cases arise from the formation of the Philadelphia chromosome. The Philadelphia chromosome is the result of a reciprocal translocation between chromosome 9 and 22, specifically t(9;22)(q34;q11)<sup>[3-5]</sup>. Currently, Imatinib or interferon  $\alpha$  are used as the primary treatment for standard risk CML<sup>[6]</sup>.

In AML, the hematopoietic progenitor cells lose their ability to differentiate normally due to a heterogeneous clonal disorder. The specific mutations associated in AML are very diverse but some common mutations are related to the *FLT3*, *NPM1*, *CEBPA*, *MLL*, *BAALC*, or *EV11* genes<sup>[7-12]</sup>. Regardless of the mutation(s), patients diagnosed with AML have difficulty producing mature erythrocytes, neutrophils, monocytes, and platelets. This is usually noticed in the patient by the inability to fight infections<sup>[13]</sup>. Induction therapy for AML includes a course of cytarabine following a course of anthracycline daunorubicin<sup>[14]</sup>. Due to different biological and clinical features compared to younger patients, treatment of older patients with AML has been hampered by uncertainties. There are suggestions that cytogenetic information is critical in order to facilitate treatment decisions for older AML patients. Such patients with adverse-risk cytogenetics derive little benefit from standard induction therapy, and an assessment of the percentage of bone marrow blasts may guide treatment decisions. Over the last few years large-scale genomic studies of patients with AML have also unveiled recurrent somatic mutations in genes involved in epigenetic regulation and the spliceosomal machinery. The identification of these mutations and their impact on prognostication has led to improvements in risk-stratification strategies and provided new potential targets for the treatment of these myeloid malignancies.

The causes of ALL include chromosomal translocations, hyperploidy of more than 50 chromosomes, and altered transcription factors. These alterations contribute to changes the cellular function of the hematopoietic stem cells<sup>[15]</sup>. The possible cellular processes damaged in ALL are the regulation of differentiation, proliferation, and cell programmed death<sup>[1]</sup>. Some of the pathways affected include the expression of *FLT3*, a tyrosine receptor kinase, which regulates the retinoblastoma pathway and cells entrance into mitosis cycle<sup>[16]</sup>. Another mutation that commonly occurs in ALL is the formation of the *TEM-AML1* fusion protein which causes deacetylation of histones. By deacetylating the histones, this inhibits differentiation of the hematopoietic stem cells by inhibiting gene transcription<sup>[17,18]</sup>. Regardless of the type of ALL, the standard induction therapy for all cases is the administration of glucocorticoids (GCs). The most commonly

used steroids are dexamethasone and prednisolone. Unlike AML, and CML, ALL has a higher incidence rate in children than in adults giving it a median age of incidence of 39 years<sup>[19]</sup>. Given the younger median age of these patients, they tend to be very resilient to the treatment over the course of therapy, and in over 80% of cases go into full remission<sup>[1,20]</sup>. Because they are unable to tolerate chemotherapy regimens as intense as those administered to children, adult ALL patients present with higher-risk features, and therefore, the overall treatment plan for adult ALL is modeled after the pediatric paradigm. This includes multi-agent chemotherapy in the forms of induction, consolidation, and maintenance. Most patients will go into complete remission but often relapse. Wealth of new information regarding the genetic alterations involved in the development of lymphoid leukemias is likely to have a significant impact on patient care as well present several important challenges and opportunities. It is likely that some genetic alterations may have a complex and unexpected role in the development of malignancies. Further, different genetic lesions can affect the same cellular pathway in different cases. Proper understanding of these genetic variations may not only provide a framework for basic research but also could convert these results into a meaningful clinical outcome.

## ROLE OF GLUCOCORTICOIDS IN LEUKEMIA

Most of the biological effects of GCs are regulated *via* the glucocorticoid receptor (GR) at the level of second messengers such as cAMP<sup>[20]</sup>. The two major GR-protein isoforms of interest in pro-inflammatory responses are the GR- $\alpha$  and GR- $\beta$ . The GR- $\alpha$  is typically associated with steroid sensitivity and acts in an agonistic manner whereas the GR- $\beta$  seems to be associated with GC mediated GR resistance and seems to act as an antagonist when bound to GC<sup>[21,22]</sup>. The GR gene lies on chromosome 5 (5q31). The GR protein contains four major functional domains: the N-terminal transactivation domain for AF1, A DNA binding domain (DBD) that contains two zinc fingers, and the C-terminal ligand binding domain (LBD)<sup>[23]</sup>. The N-terminal transactivation domain contains the AF1 domain and is responsible for transcriptional activation of target genes<sup>[24]</sup>. The first zinc finger binding domain contains the AF1 and nuclear factor  $\kappa$ B binding domains and is involved in the transrepression of the receptor<sup>[25]</sup>. The second zinc finger domain contains the genes that regulate receptor dimerization and glucocorticoid response element mediated transactivation<sup>[26-29]</sup>. The LBD contains a pocket for steroid binding, a nuclear localization signal, and small but potent ligand-dependent transactivation region (AF2), which interacts with a specific set of co-activators or co-repressors. The determination of AF2 co-activation/co-repression activation depends on the orientation of the AF2 binding, which is based on whether the LBD is activated by an agonist or an antagonist to LBD<sup>[30,31]</sup>. Due to their lympholytic actions, GCs are included in many therapeutic regimens for

the treatment of various forms of leukemia and lymphoma<sup>[32,33]</sup>. It is clear that the presence of adequate quantities of properly functioning GR is a necessary but not solely sufficient component for lymphocytolysis<sup>[34,35]</sup>. In chronic lymphocytic leukemia, certain types of childhood ALL, and malignant lymphomas, a correlation between response to GC therapy and functional GR levels assayed by ligand binding has been found<sup>[36,37]</sup>. However due to the diversity of these diseases, coupled with their relative individual rarity, no simple overall correlation was found between GC activity and activation of lymphocytolysis.

## STEROID-RESISTANCE

Although a significant number of ALL patients respond well to GCs, some reveal primary GC resistance, and those sensitive to GCs almost exclusively develop secondary resistance after prolonged GC therapy<sup>[38]</sup>. There are two forms of resistance, primary and secondary. Primary resistance is due to an inherent GC resistance. This can be related to the level of GR expression and the regulation of intracellular substrate availability<sup>[39]</sup>. The second form of steroid resistance is developed over the course of treatment and can take multiple forms. Within the developed resistance, B-cell lineages and T-cell lineages seem to have divergent mechanisms of resistance. Though the mechanism of this resistance has not been completely elucidated, it was once thought that the resistance was due to an alteration in GR expression that is induced by GC treatment. However, later studies found this not to be the sole cause of the resistance<sup>[40]</sup>. Another proposed mechanism of resistance involves the B-cell lymphoma family of proteins<sup>[41]</sup>. Large clinical surveys suggest a correlation between functional GR expression levels and primary GC sensitivity and prognosis<sup>[42,43]</sup>. GC-resistance is either a familial or sporadic condition that can be characterized by generalized end-organ inability to respond to normal GC levels<sup>[44]</sup>. Thus, steroid resistance in leukemia is a major problem in ALL as it is the primary induction therapy in childhood. Without GC sensitivity the leukemic cells are no longer induced into apoptosis by the treatment.

The BCL2 family of proteins is critical in the regulation of apoptosis induced by cellular stress. BCL2 family of proteins can have either pro-apoptotic or pro-survival properties. Though the signals control opposing functions, they are related through conserved sequence motifs. These motifs are the BCL2 homology domains (BH). The high affinity BH1 and BH2 domains, a pro-survival specific motif, interacts with the pro-apoptotic BH3 domains, inhibits the death signaling pathway allowing for cell survival<sup>[45]</sup>. The opposing pathway, induced by BH3, induces cell death *via* the BCL2 pathway. It is induced by the activation of the BCL2-associated X protein (BAX) and BCL2 homologous antagonist/killer (BAK). The activation of the BAX/BAK pathway leads to apoptosis *via* permeation of the mitochondrial membrane<sup>[46]</sup>. However, when BCL2 and BCL2 extra-large (*MCL-1*) knockdowns

were induced, GC administration showed no effect on cell viability when cells from a child ALL patient were used. This indicated that the mechanism of GC resistance lies downstream of BCL2 and MCL-1 pathways<sup>[47]</sup>.

Another possible cause of resistance in ALL patients could be due to an over expression of 11 $\beta$ -HSD. The function of this protein is to inactivate GC as they enter the cell. In rats that have been undergoing dexamethasone therapy and are sensitive to GCs, it has been found that their circulating levels of 11 $\beta$ -HSD1 are elevated. However, once they become resistant to GCs, their levels of 11 $\beta$ -HSD1 are significantly decreased even in the presence of dexamethasone<sup>[48]</sup>. As a result, inhibitors of 11 $\beta$ -HSD, such as carbenoxolone, have been shown to improve cell death in the T-cell leukemic cell line, CCRF-CEM<sup>[49]</sup>. This suggests that 11 $\beta$ -HSD inhibitor could be used as part of a combination therapy in ALL.

## SUMMARY AND PERSPECTIVES

It has been reported that several point mutations in the LBD of the human GR develop in steroid-resistant leukemic patients, which interferes with GR's ability to bind GCs and subsequently interferes with gene regulation. GC-based therapy is still the most commonly used treatment to combat chronic and acute inflammation. Due to multiple physiological actions of GC/GR, a chronic exposure to pharmacological GC doses becomes a problem in therapeutic settings, causing undesirable, yet on-target effects. Therefore the real challenge is not only to develop more specific GR-ligands, but to change the spectrum of GR-mediated events and try to skew it more towards desired pathways. Therefore, the mainstay of research efforts must be focused on further characterizing the mechanisms of GR actions in detail and developing new therapeutic strategies to fight leukemia with a better benefit-to-risk-ratio. We must aim to dissect certain important determinants of GC/GR signaling in clinical contexts that can be applied for designing of more specific and better targeted therapies to combat leukemia.

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- 3 Tian D, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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- 4 Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

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- 5 Vallancien G, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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- 7 Geraud G, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

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- 8 Banit DM, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

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- 9 Outreach: Bringing HIV-positive individuals into care. *HRS-A Careaction* 2002; 1-6 [PMID: 12154804]

### Books

*Personal author(s)*

- 10 Sherlock S, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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*Author(s) and editor(s)*

- 12 Breedlove GK, Schorheide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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- 13 Harnden P, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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*Electronic journal (list all authors)*

- 15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05;

1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

#### Patent (list all authors)

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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