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Multidrug Resistance Mechanism of Acute Lymphoblastic Leukemia

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1. Introduction

Multidrug resistance is recognized as the key factor of many anticancer drugs invalidity. Anticancer treatments such as chemotherapy or radiation must hit their cellular targets and then cause cellular alteration or damage. However, in most cases the damage inflicted by the anticancer agent triggers apoptosis [1]. Acute lymphoblastic leukemia (ALL) is the most frequently occurring cancer in children. Chemotherapy to childhood ALL has markedly improved during the past years [2]. The remission rate of chemotherapy patients is more than 95%, and the long term free survival rate about 75-80%. However, 25–30% of the patients will experience a relapsing, that leads to die of teenagers. Which may be explained by unfavourable pharmacokinetics, by leukemic stem cells regrowth and by cellular drug resistance [2, 3].

Since the early 1970s, multidrug resistance (MDR) has been known to exist in cancer cells and is thought to be attributable to a membrane-bound, energy-dependent pump protein (P-glycoprotein [P-gp]) capable of excluding various related and unrelated chemotherapeutic drugs. In this chapter, we would discussed the multidrug resistance mechanism of cancer cell.

2. Prognostic factors

Prognosis of patients with ALL depends on several interrelated factors including sex, age, race, leukocyte burden, immunophenotype, and chromosomal abnormalities, central nervous system (CNS) involvement and response to therapy [4-7]. It is important to recognize prognostic factors depending on the efficacy of therapy; more effective regimens decreasing the importance of prognostic variables. And identification of prognostic factors has become an essential element in the design and analysis of current therapeutic protocols in ALL. The biologic explanation of the prognostic significance of these features is unclear, but is often assumed to be related to cellular drug resistance [8, 9].

Age is an important but complex risk factor in ALL [10-12]. Children aged 2 to 10 years have the best prognosis. Adults and infants younger than 12 months of age have the worst prognosis. The poor prognosis in infants is most likely related to a higher incidence of undifferentiated and hybrid leukemias [8, 13, 14]. For adults, increasing age is associated with

lower remission rates and shorter remissions. To analyze results of any therapeutic trial, it is important to consider the age limits and distribution, since these factors have a major effect on outcome.

The initial leukocyte burden is the most important conventional predictor of clinical outcome. There is a linear relationship between the initial leukocyte counts and outcome in children with ALL. Children with high leukocyte count tend to have a worse prognosis. Although there is no sharp dividing line, patients with an initial leukocyte count more than 50000 cells/mm^3 blood are universally recognized as having a particularly poor prognosis; however, the worst survival experience was exhibited by those with initial leukocyte from 100000 – 200000 cells/mm^3 blood.

Immunophenotype is one of the prognostic factors in ALL. B-ALL cases had the worst prognosis; although this has improved, while patients with B cell precursor ALL have the most favourable prognosis. Among the patient with B cell precursor ALL, those with the early pre-B cell phenotype have a more favourable prognosis compared with patients with pre-B cell phenotype, who have a relatively poor prognosis [15, 16]. T cell ALL is usually associated with male, sex, high leukocyte count, mediastinal mass, and CNS infiltration, and formerly had a poor outcome [17-21].

Chromosomal abnormalities can be identified at least 80% to 90% acute childhood leukemia [22]. The karyotypes of leukemic cells not only have diagnostic and prognostic importance but may also indicate the sites of molecular lesions involved in leukemic transformation and proliferation. Childhood ALL can be classified by the number of chromosomes/leukemic cell. Although several ploidy groups have been recognized, only two have clinical relevance. Hyperdiploidy (>50 chromosomes/cell) is associated with a better prognosis than that indicated by more traditional measures [23]. The biologic basis for the association between ploidy and prognosis is not yet clear but may stem from the tendency of hyperdiploid blasts to accumulate increased amounts of methotrexate and its polyglutamates as well as the marked propensity of these cells for apoptosis. Hypodiploidy (<45 chromosomes) is associated with an exceptionally poor prognosis. Phenotype-specific reciprocal translocations are the most common cytogenetic hallmarks of the childhood leukemias [24-28]. The majority of rearrangements are well characterized both clinically and molecularly and are thought to have a causative role in leukemogenesis. Chromosomal rearrangements can contribute to leukemia by moving proto-oncogenes into the vicinity of normally active enhancer or promoter sequences. the prototype of this mechanism is t(8;14)(q24;q32.3) in B-cell ALL, which brings the MYC proto-oncogene on chromosome 8 under the control of immunoglobulin-gene regulatory sequences on chromosome 14. Through a series of complex molecular changes, including coincident mutations, MYC is dysregulated, leading to inappropriately increased expression of the MYC product, a nuclear regulatory protein (transcription factor) that interacts with the other cellular protein (MAX) to influence the expression of other genes involved in cellular proliferation [29, 30]. A similar mechanism operates in T-cell ALL.

The BCR-ABL gene in ALL, which results from the classic t(9;22)(q34;q11) translocation that forms the Philadelphia chromosome, is perhaps the best known fusion gene in the childhood leukemias. In adult-type chronic myelogenous leukemia (CML) , the Philadelphia chromosome gives rise to a 210kd BCR-ABL product, whereas in most cases of childhood ALL with this rearrangement, the breakpoint within the BCR region is more centromeric,

yielding a smaller (185 kd) chimeric protein [31]. Both proteins are tyrosine kinases, but the 185 kd form has more potent transforming activity. Regardless of the type of BCR-ABL protein, blast cells with the Philadelphia chromosome show extraordinary resistance to chemotherapy.

Approximately one fourth of patients with pre–B-cell ALL have a t(1;19)(q23;p13) translocation, which fuses the E2A gene on chromosome 19 with the PBX1 gene on chromosome 1.19. Paradoxically, the chimeric transcription factor induces both proliferation and apoptosis of lymphoid cells in transgenic mice [32, 33].

Structural chromosomal abnormalities affecting the q23 region of chromosome 11 are common in the acute childhood leukemias. Approximately 5% all children with ALL and 70% infants have 11q23 rearrangements, primarily the t(4;11)(q21;q23) translocation. This rearrangement, which creates the MLL-AF4 fusion gene, is associated with hyperleukocytosis and a poor prognosis. In fact, the extremely poor outcome of treatment in infants with ALL appears to be limited to those with the t(4;11) translocation or other 11q23 abnormalities.

3. Drug resistance

As mentioned previously, the prognostic significance of these factors may partly be caused by cellular drug resistance. Cellular drug resistance is generally recognized as an important determinant of the clinical outcome after chemotherapy. Even if optimal tumor cell exposure is achieved, a number of cellular factors may be responsible for drug resistance. The mechanisms would be described as following:

3.1 Drug transporters mediate resistance

Classical resistance is associated with transmembrane protein-mediated efflux of cytotoxic compounds leading to a decreased cellular drug accumulation and toxicity. Most of them belong to ATP-binding cassette (ABC) transporters superfamily including P-glycoprotein, multidrug resistance-associated protein (MRP) family, breast cancer resistance protein (BCRP), lung resistance protein (LRP) *et al*.

3.1.1 P-glycoprotein (P-gp)

P-gp expression occurs in about 30% acute myeloid leukemia (AML) patients at diagnosis and >50% at relapse and correlates with a reduced complete remission rate and shorter duration of survival of the patients. P-gp expression is also observed in CML blast crisis, chronic lymphocytic leukemia (CLL), multiple myeloma, non-Hodgkin's lymphoma and in ALL [34].P-gp is a member of the ABC (MDR/TAP) subfamily. In humans, P-gp is encoded by two MDR genes, including MDR1 and MDR3,which are located on the long arm of chromosome 7 (7q21) [35]. Human P-gp is a 170 kDa polypeptide, consisting of 1280 amino acids. The protein appears to have arisen by a gene duplication, fusing two related half molecules, each consisting of one nucleotide-binding domain and one transmembrane domain. The multidrug-resistant phenotype is associated with MDR1. However, under certain conditions, human MDR3 may transport selected MDR1 substrates, albeit inefficiently [36-41].

P-gp primary sequence displays 3 putative glycosylation sites in a region that appears to lie in the first extracellular loop of the protein; however, it seems unlikely that glycosylation

affects the function of P-gp because of tunicamycin treatment, which blocks N-linked glycosylation, does not alter drug sensitivity in human multidrug resistant cells. P-gp has been shown to be phosphorylated on several sites through several kinases, including protein kinase C and the cAMP-dependent protein kinase A. Phosphorylation of P-gp appears was also associated with drug resistance. Indeed, treatment with the phorbolester TPA, which stimulates P-gp phosphorylation, results in increasing drug resistance and decreasing drug accmnulation in some multidrug-resistant cell lines. By contrast, protein kinase inhibitors, such as staurosporine, decreased phosphorylation and impaired anticancer drug transport [42, 43].

P-gp has a wide variety of substrates. All its substrates are large hydrophobic and amphipathic molecules, although they have no structural dissimilarity. These molecules are able to intercalate into the membrane and enter the cytosol by passive diffusion. It is no longer believed that P-gp is a classical pump, which binds substrates from the extracellular fluid and then transports these over the membrane. Hydrophobic compounds that are substrates for P-gp do not fully penetrate into the cytoplasm of cells that express P-gp [44]. Interaction of substrate with P-gp has been shown to take place within the membrane[21]. This mechanism of transport is also postulated for a prokaryotic homologue of P-gp with a similar broad substrate specificity in Lactococcus lactis. However, the exact mechanism by which this protein removes hydrophobic drugs from the cell is still unclear. It may translocate drugs actively from the cytosolic inner lipid leaflet of the plasma membrane to the outer lipid leaflet. Then these drugs are able to leave the plasma membrane by diffusion.

Besides anti-cancer drugs, P-gp also mediates the transport of various structurally unrelated compounds including toxic peptides, such as gramicidin D, valinomycin and N-acetyl-leucyl-leu -cyl-norleucinal (ALLN), digoxin, opiates, fluorescent dyes. Endogenous compounds, such as some steroid hormones, have also been demonstrated to be substrates for P-gp. In addition, the pump may serve as an ATP channel and is involved in volume-regulated chloride channel activity. A great number of studies have been conducted during the last few years to analyze the relation of P-gp expression and hematological malignancies, then to determine its clinical relevance. Various methods for determining P-gp gene expression have been used, such as northern blot, dot blot, RNase protection assay, hybridation and RT-PCR. In addition, western blot, immunohistochemistry and flow cytometry (FCM) were also used to analyze P-gp protein level. Furthermore, P-gp activity has also been evaluated by FCM.

Mutational analysis of P-gp has indicated that some point mutations may result in altering drug transport activity. Indeed a change Gly185Val led to reduce vinblastine transport, whereas colchicine transport was improved. However, two different groups showed that a mutation of the major phosphorylation sites within P-gp doesn't affect its transport function.

3.1.2 MRP

The human MRP1 gene is mapped to chromosome16p13.1[45-47]. It encodes a membrane-bound glycoprotein consisting of 1531 amino acids. This protein has a similar topologic structure to that of P-gp. However, in addition to the two half transporters connected by a linker region L1 as in P-gp, MRP1 protein contains an extra N-terminal segment, TMD 0, which connects TMD1 with a L0 linker region. The L0 linker region is essential for drug transport, whereas TMD0 is not required for transport. Although MRP1 also requires two ATPs as the energy source to transport chemotherapeutic drugs, the mechanism in the cycle of transportation is somewhat different from that of P-gp. In P-gp, the functions of the two NBDs are “equal”, and the two

ATP-binding sites operate randomly but alternately. In MRP1, the function of NBD1 and NMD2 is nonequivalent. NBD1 has higher affinity than NBD2 for ATP. Therefore, when the substrate binds to TMDs of MRP1, the conformational change of MRP1 protein first induces ATP binding at NBD1. It then further alters the conformation of the protein and enhances ATP binding at NBD2. When both NBD1 and NBD2 are occupied by the two ATPs simultaneously, the bound substrate is transported out of the cell. After substrate extrusion, the ATP bound at NBD2 is hydrolyzed first. The release of ADP and inorganic phosphate from NBD2 partially brings the MRP1 protein back to its original conformation, and facilitates the dissociation of ATP bound at NBD1. Subsequent release of ADP and inorganic phosphate from NBD1 returns the MRP1 protein to its original conformation.

MRP1 is expressed almost ubiquitously in many different organs and cell types. Unlike P-gp, which is invariably located in the apical membranes of epithelial cells, MRP1 is located basolaterally and tends to pump drugs into the body, rather than excrete them into the bile, urine or gut. Cells overexpressing MRP1 protein are resistant to a variety of anticancer drugs, e.g. doxorubicin, epirubicin, vinblastine, vincristine, andetoposide. However, MRP1 cannot transport the unmodified anticancer drugs without the presence of glutathione (GSH). This implies that MRP1 may cotransport the anticancer drugs with GSH, or GSH may bind to the MRP1 protein to enhance the transport of these hydrophobic anticancer drugs across biological membrane.

3.1.3 BCRP

The initial demonstration that BCRP transfection directly confers MDR supports evidence that BCRP might be able to function by homodimerization [48-50]. The exogenous BCRP proteins migrated as 70 kDa bands in SDS–PAGE under reducing conditions, but as a 140 kDa complex in the absence of reducing agents. The 140 kDa BCRP complex dissociated into 70 kDa polypeptides with the addition of 2-mercaptoethanol. The 140 kDa BCRP complex was immunoprecipitated with anti-Myc antibody from lysates of cells co-transfected with Myc- and HA-tagged BCRP constructs. The 140 kDa complex reacted with anti-HA and anti-BCRP antibodies. After the addition of reducing agents, a 70 kDa BCRP band was seen, reactive with both anti-HA and anti-Mycantibodies. Furthermore, a dominant-negative mutant of BCRP was found to inhibit BCRP function partially when cotransfected with BCRP. These results elegantly demonstrate that BCRP forms a homodimer bridged by disulfide bonds. A molecular mass shift from a 72 kDa band under denaturing conditions to a 180 kDa band after treatment with crosslinking agents was also noted using polyclonal antibodies directed against peptide epitopes of BCRP.

The BCRP promoter is TATA-less, contains a CAAT box. Unlike ABCG1 promoter, the BCRP promoter does not contain a sterol response element, strengthening the argument that BCRP is not involved with lipid transport. The reporter analysis indicated that a 312 bp sequence directly upstream from the transcriptional start site conferred basal promoter activity, with positive and negative cis-regulatory elements identified in the region between 1285 and 1362 relative to the transcriptional start site. Strong resistance to mitoxantrone characterizes most drug-selected cell lines that overexpress BCRP, even if the selecting agent is not mitoxantrone.

3.1.4 LRP

LRP also known as the major vault protein (MVP), is not an ABC transporter but it is frequently expressed at high levels in drug-resistant cell lines and tumor samples [51, 52].

LRP/MVP is the most abundant component of the vault complex. Vaults are ribonucleoprotein (RNP) particles that are present in the cytoplasm of most eukaryotic cells and might be involved in intracellular transport processes. However, the physiological role of vaults is poorly understood.Vaults might confer drug resistance by transporting drugs away from their intracellular targets and/or by the sequestration of drugs. Several studies showed that LRP/MVP expression was an independent adverse prognostic factor for response to chemotherapy. With regard to clinical drug resistance, LRP/MVP expression in AML, multiple myeloma and diffuse large B cell lymphoma was associated with poor response to chemotherapy. LRP/MVP is an indicator of poor response to chemotherapy with platin or alkylating agents.

3.2 Resistance related to cell death mechanisms and apoptosis

Many investigators have considered apoptosis as the essential response of cancer cells to chemotherapeutic agents. Many data supported the association of functional apoptotic pathways in cancer cells with chemotherapy sensitivity. The discovery of the bcl proteins family altered the threshold of recognition of cell damage as a cell death signal, which suggests novel mechanisms of MDR [46, 49, 53-56]. The anti-apoptotic protein bcl-x_L and bcl-2 were strong associated with drug resistance.

Bcl-2 gene, discovered by Tsujimoto and Croce, is widely expressed in human tumor. Bcl-2 gene is translocated in many follicular B cell lymphomas from its normal 18q21 position to 14q32 where its location adjacent to enhancers in the immunoglobulin H gene leads to high level expression. Alternative splicing yields two proteins, bcl-2a and bcl-2b, differing only at their C terminus. Bcl-2 inhibited cell death and altered the normal cell death versus cell division ratio, which may allow tumor cells to accumulate the mutations, then cause the cells to become invasive and metastatic. Most publications about bcl-2 showed that transfection of immature pre-B cells with bcl-2 expression vectors protected against cell death due to IL-3 deprivation, thus indicating a role in antagonizing apoptosis.Transfection and antisense experiments confirmed an important role for bcl-2 in resistance to apoptosis induced by chemotherapeutic drugs. It is clear that bcl-2 is just one component of a large and complex family of proteins which determine particular cells die in response to particular physiological or pharmacological environments (e.g. growth factor deprivation, drug exposure). Apotosis may be particularly important in determining organ shape and size during development.

More recent research indicates a key role of bcl-χ_L in apoptosis regulation in follicular lymphoma. Transfection with bcl-χ_L cDNA has been shown to protect several cell types *in vitro* against apoptosis induced by a wide range of chemotherapeutic drugs. Transfection human bcl-χ_L cDNA into the murine IL-3-dependent prolymphocytic cell line FL5.12, then increased resistance to the anticancer drugs bleomycin, cisplatin, etoposide and vincristine.

3.3 Telomerase involved in resistance

Telomerase is responsible for the renewal of the chromosomal ends, the so-called telomeres [57]. By preventing them from **shortening** with each cell cycle, telomerase is able to inhibit cellular senescence and apoptosis. Telomerase activity, which is detectable in the majority of cancer cells, allows them to maintain their proliferative capacity. The thus obtained immortality of those cells again is a key to their malignancy.

3.4 DNA mismatch repair deficiency led to resistance

DNA mismatch repair deficiency results in a high risk of malignant tumorigenesis [58-61]. A defect in this system may cause accumulation of mutations in several proto-oncogenes or tumor-suppresser genes, which results in the transformation to cancer. DNA mismatch repair deficiency was thought to be an early event in multi-step carcinogenesis. It could be speculated that an abnormality in the DNA mismatch repair system increases the risk of multidrug resistance.

DNA damage caused by cisplatin is recognized by DNA damage recognition proteins, such as high mobility group proteins (HMG1 and HMG2) and mismatch repair complexes (hMSH2 or hMutSα), which transducer DNA damage signals to various downstream effectors.Cell death or cell survival after DNA damage depends on the relative intensity of the signals generated and the crosstalk between the effectors involved. Among these effectors, the p53 tumor suppressor gene plays a central role in determining the final fate of the cell. DNA damage recognition proteins activate the mitogen-activated protein kinase signal transduction pathway, which activates the function of p53 and causes cell cycle arrest at the G2/M checkpoint for DNA repair [60, 62-65]. If the DNA damage is too excessive to repair, apoptosis occurs through the bax and caspase system. In addition, DNA damage may also result in apoptosis through the p53-related gene, p73. The other mechanisms involved in the resistance include enhanced DNA repair capacity and increased antiapoptotic activity.

3.5 Leukemia stem cell contribute to resistance

Current investigations in the field of cancer multidrug resistance research intensively focus upon the "cancer stem cell (CSC) [66-68]". The CSC theory appears to be well established and now widely accepted. The CSC, similar to a normal stem cell, is capable of self-renewal and the production of differentiated progeny. In addition, the human CSC has a capacity to form secondary tumors. Such features of CSCs reflect the activity of cancer initiation, therapy-resistance, all of which are critical in cancer therapy. Stem cells are primarily characterized by the properties of unlimited self-renewal, which maintains and expands the undifferentiated cell pool over the lifetime of the host, and multi-lineage differentiation, which produces progeny of diverse mature phenotypes to generate and regenerate tissues. These stem cell attributes are tightly regulated in normal development, yet their alteration may lead to many human diseases ncluding cancer. In fact, because stem cells and some cancer cells share self-renewal and differentiation capacities, it was suggested that tumors were derived from mutated stem cells, "called cancer stem cells" [69-72]. Although this hypothesis was postulated in early reports, definite proof of their existence came from recent studies in leukemia, where among the complete tumor cell population only a small subset of cells could initiate, regenerate and maintain the leukemia after transplantation into immunocompromised mice. Using similar functional approaches, a variety of cancer stem cells have been identified in an increasing number of epithelial tumors, including breast, prostate, pancreatic, and head and neck carcinomas, all of which were distinguished by the expression of the cell-surface glycoprotein CD44. Another cell surface marker, the CD133 glycoprotein, defined the tumor-initiating cells of brain and colon carcinomas.The concept of cancer stem cells is not only changing our current understanding of cancer biology, but may also have profound consequences on cancer diagnostics and therapeutics.

Cancer stem cells have been identified in leukemias. Many researchers now suspect that all cancers are composed of a mixture of stem cells and proliferative cells. These cancer stem cells make up as few as 1% of the total tumor cells, making them difficult to detect and study. Therefore, the existence of cancer stem cells provides a tumor reservoir that is the source of disease recurrence and metastasis. ABCB1 and ABCG2 genes are expressed in most tumor stem cells [41, 73]. Thus, the major barrier to therapy is the quiescent tumor stem cell with constitutive MDR. In fact, dose-limiting toxicities of many antineoplastic agents occur precisely at drug concentrations that damage normal tissue stem cells. If the proposed relationships between normal and neoplastic stem cells prove correct, the inescapable conclusion is that systemic cytotoxic therapies are doomed to failure because regimens that spare resting normal stem cells will also likely spare resting tumor stem cells. Similarly, inhibition of drug transporters may also cause toxicity of the patient's normal stem cells, particularly those of the bone marrow. Successful therapy awaits the discernment of biological and immunologic differences between the tumor and normal stem cells so that approaches can be developed to eliminate thetumor stem cells without excessive toxicity to normal stem cells, which can be measured *in vitro*.

General decreased transport of drug into the cell, defective intracellular metabolism of the drug to its active compound, increased drug inactivation, enhanced cellular repair mechanisms, altered target molecules, altered cell death regulators could increased MDR. Because many drugs are used in the treatment of leukemia and many factors may be responsible for resistance to each drug, it is unlikely that one single mechanism is responsible for clinical resistance to the complete treatment. And the resistant mechanism to some drugs were listed as following (Table 1).

4. Drug resistance assay

There are many different assays to asses the chemosensitivity of leukemia cells. Clonogenic assays have long been considered to be the golden standard for chemosensitivity testing *in-vitro* [74-76]. However, there were a number of drawbacks. Firstly, the number of patient samples of which the leukemic cells will be clonogenic is limited, especially in ALL samples *in vitro*. Secondly, the drug effect is measured on a small proportion of cells, *i.e.* those cells that can be induced to proliferation *in vitro*, and not on cells that are non dividing or resting. Practical disadvantages are that these assays are very time consuming and laborious. Therefore, these drawbacks make clonogenic assays less suitable for its use in ALL patients.

Recently, non clonogenic assays, an increasing number of authors has been studying cellular drug resistance in childhood leukemia. Examples of these assays are the colorimetric tetrazolium based assays such as the MTT, INT [77-79], DiSC [80], and the fluorometric microculture cytotoxicity assay (FMCA)[81]. The DiSC assay relies on the intactness of the cell membrane in living cells as opposed to dead cells after several days of incubation with drugs. Relatively low numbers of cells are needed to test a range of drugs in different concentrations. A main advantage of this assay is that it can discriminate between malignant and non-malignant cells, in contrast to the MTT assay and FMCA. However, the DiSC assay has the disadvantages of being subjective, laborious, and time consuming, which makes it less suited for large-scale patient studies.

Since drug resistance has a major impact on the success of chemotherapy, it is of clinical importance to identify possibilities to modulate or circumvent each type of drug resistance,

which contribute to decreasing the unnecessary toxicity of drugs and increasing the efficacy of treatment by a more rational design of effective chemotherapies.

Type of Drug	Possible Mechanisms
Glucocorticoids (GC)	Affinity of receptor Function of receptor Nuclear translocation of the GCR complex DNA binding of the GC R complex GCR polymorphism (?)
L-Asparaginase	Asparagine synthetase Membrane transport
Methotrexate (MTX)	MTX polyglutamylation and folylpolyglutamate synthetase (FPGS) / folylpolyglutamate hydrolase Active efflux Intracellular normal folate pools Dihydrofolate reductase, Thymidylate synthase (TS) Methylenetetrahydrofolate reductase(MTHFR) (?)
Thiopurines	Nucleoside concentration, ecto-5′ nucleotidase Cyto-5′ nucleotidase and phosphatases Phosphoribosyl pyyrophosphate (PRPP) and PRPP Amidotransferase Hypoxanthine-guanine phosphoribosyl transferase Thiopurine methyltransferase (TPMT)
Cytosine arabinoside (ara-C)	Ara CTP formation Ara C transport Ara-C and Ara-CTP deamination DNA incorporation
Anthracylines, Vinca-alkaloids and Epipodophyllotoxins	MDR-1/P-glycoprotein Multidrug resistance related protein (MRP) Lung resistance protein (LRP) Topoisomerase II BCRP (breast cancer resistance protein)
Alkylating agents	Glutathione Glutathione and glutathione S-transferases DNA repair

Table 1. Drug resistance mechanisms in ALL

5. References

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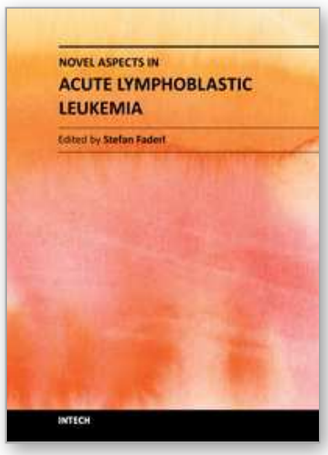

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Acute lymphoblastic leukemia (ALL) has turned from a universally fatal to a highly curable disease in little more than four decades. Even though differences in outcome continue to exist between children and adults, intense efforts are under way to overcome this discrepancy and improve the prognosis of adult patients as well. This exemplary progress in ALL therapy has been possible by the combination of an increasingly better understanding of the biology of the disease, availability of a range of effective drugs, and astute designs and relentless executions of many clinical trials. ALL is a complex disease requiring complex therapy. Whereas this book cannot provide a comprehensive review of every one of its many facets, the chapters from many investigators from around the world nevertheless cover a number of relevant topics: aspects of the epidemiology of ALL in Hispanics, ophthalmologic manifestations of ALL, overviews of current therapy and drug-resistance mechanisms, novel biological pathways and targets, new drugs in development, and long-term consequences of CNS prophylaxis and therapy. The publishers and editor therefore hope that the prospective readers will find enough insight and information for their own endeavors.

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