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## Chemotherapy Toxicity in Patients with Acute Leukemia

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### 1. Introduction

During the treatment for acute leukemia (AL) a patient may experience a wide variety of complications that mainly have three possible origins, namely the disease itself (leukemic infiltration), peripheral blood cell depression (because of hemorrhagic or infectious processes) and toxicity induced by chemotherapy.

The toxicity of chemotherapy is a common cause of morbidity and mortality in cancer patients, as well as a frequent source of sequelae at mid-long term. These adverse effects are often the consequence of direct toxicity in healthy tissue, as a result of the low specificity displayed by these drugs. Furthermore, and regardless of their specificity, these compounds may also exacerbate complications derived from the tumor growth, as it is the case of pancytopenia or the *Tumor Lysis Syndrome*. Chemotherapy toxicity becomes more frequent as the treatment is intensified, thus challenging the clinician with both diagnostic and therapeutic problems. In this chapter we will discuss the major clinical signs of toxicity produced by chemotherapy drugs in patients with AL. Hematological and gastrointestinal (mucositis, nausea and vomiting) adverse effects will not be included, as their description suits better in an *Initial Management* chapter. In the last section of this chapter we will discuss recent data on whether pharmacogenetics may help individualize the therapy for AL, thus avoiding serious toxicity.

### 2. Cardiotoxicity

Cardiovascular abnormalities in patients with AL usually result from derangements in metabolic, electrolyte, and pulmonary function. Because leukemic infiltration of the heart is rare, the majority of cardiovascular problems in AL patients are chemotherapy-related toxicities produce by anthracyclines (Pihan, 2009).

Anthracycline chemotherapy is associated with *acute effects* (occurring during and shortly after administration), e.g. electrocardiographic alterations including prolongation of QT interval, development of ventricular late potentials and various arrhythmias (Bagnes et al., 2010); *subacute effects* (noted within days or weeks of administration) consisting of toxic

myocarditis or pericarditis and *chronic effects*, which occur weeks or months after administration and manifest as cardiomyopathy. Cardiomyopathy is a multifactorial process related to oxidative stress and myocyte induction of apoptosis. Our inability to predict and prevent anthracycline cardiotoxicity is, in part, due to the fact that the molecular and cellular mechanisms remain controversial and incompletely understood (Sawyer et al., 2010).

At a cumulative dose of 550 mg/m<sup>2</sup> doxorubicin more than a quarter of patients develop congestive heart failure (CHF). This complication can take place at lower doses in susceptible individuals such as elderly, children, subjects with prior cardiac disease, and those who have had previous mediastinal irradiation (Ng et al., 2006). In the pediatric population, cardiomyopathy can occur at cumulative doses of 300 mg/m<sup>2</sup> (given as daunorubicin equivalent) (Creutzig et al., 2007). In addition, the long-term effects of cardiac damage are more apparent in children. In a study of long term survivors of childhood cancers, cardiac mortality was shown to be the second most likely cause of death following malignancy (Creutzig et al., 2007).

There are different techniques utilized to monitor for cardiotoxicity:

1. Endomyocardial Biopsy (EB), which was traditionally viewed as the gold standard test, is actually an impractical means of monitoring due to the invasive nature of test.
2. Evaluation of left ventricular ejection fraction (LVEF) with two-dimensional echocardiography (2D-ECHO) or radionuclide ventriculography remains the most pragmatic monitoring technique. Calculation of the LVEF by 2D-ECHO is slightly more difficult; however, the fact that radiation is not used makes it more suitable for the pediatric population.
3. Other techniques have also been tested: Antimyosin antibody scintigraphy is a marker of cardiac damage, but its high sensitivity may produce positive results at very low cumulative doses of anthracyclines, thus limiting its clinical utility (Valdes Olmos et al., 2002). Cardiac troponins and natriuretic peptides, the most commonly used biomarkers of myocardial destruction and ventricular dysfunction respectively, have also been studied for this purpose (Germanakis et al., 2008).

Pretherapy baseline evaluation of LVEF is recommended for all patients with AL before starting induction therapy. However, unless the patient is known or suspected to have a cardiac disease, the treatment does not need to be delayed pending the results of LVEF (Pihan, 2009). Dose exposure should be reduced in patients with a baseline LVEF of less than 50% or in those with a 10% LVEF decline from baseline to final values below 50% (Schwartz et al., 1987).

Different anthracyclines have different patterns of toxicity (Table 1). However, changing to a different anthracycline does not substantially modify the risk for cardiotoxicity. In an attempt to reduce this adverse effect, liposomal doxorubicin has been developed. Most studies with liposomal doxorubicin have been performed in women with metastatic breast cancer. In this population, liposomal doxorubicin has shown equivalent efficacy to doxorubicin with a reduced rate of cardiotoxicity (Batist et al., 2001).

Several meta-analysis have studied the influence of different anthracyclines or different dosage schedules on the risk of cardiotoxicity in adult patients with cancer. These studies support the administration of a 6-hour (or longer) infusion (van Dalen et al., 2009), and the use of liposomal-doxorubicin over doxorubicin (van Dalen et al., 2010). It is of note that both studies agree in that there is insufficient evidence to implement such measures in children

or in patients with leukemia. In this regard, a meta-analysis with data retrieved from trials in children with ALL that randomized anthracyclines or measures to reduce cardiotoxicity, found no significant differences regarding type of anthracycline, method of administration or use of cardioprotectants (Childhood ALL Collaborative Group, 2009).

Because one of the proposed mechanisms of anthracyclins cardiotoxicity involves the generation of free iron radicals, dexrazoxane, by its iron chelating effect, confers a significant reduction in the risk of cardiotoxicity. A meta-analysis by Van Dalen et al concluded that if the risk of cardiac damage is expected to be high, it might be justified the use of dexrazoxane in patients with cancer treated with anthracyclines (van Dalen et al., 2008). In children with AL, the use of dexrazoxane seems safe and provides long-term cardioprotection without compromising oncological efficacy. Currently, in the absence of more data, the use of dexrazoxane might be justified in children if the risk of cardiac damage is expected to be high (Lipshultz et al., 2010).

### 2.1 Treatment of cardiomyopathy

The natural history of Anthracyclines cardiomyopathy, as well as its response to modern CHF therapy, remains poorly defined. Hence, evidence-based recommendations for the management of this form of cardiomyopathy are still lacking. Progress in treatment of cardiac failure, in particular the availability of drugs as angiotensin converting enzyme (ACE) inhibitors, spironolactone and beta-blokers and the current practice of monitoring cardiotoxicity, may explain the improved prognosis of this complication that, in early retrospective studies, had a mortality rate of more than 40%. The prophylactic use of enalapril resulted in the reduction of cardiac function deterioration. A recent study has shown that when this therapy is initiated soon after detection of LVEF impairment, there are more patients who present LVEF recovery and cardiac event reduction (Cardinale et al., 2010). These results show the importance of monitoring cardiotoxicity in all patients treated with anthracyclines in order to (i) identify early heart damage and (ii) begin treatment before the onset of CHF.

Among the newest compounds, symptomatic or asymptomatic QT aberrations have been reported with tyrosine-kinase inhibitors (Bagnes et al., 2010) and arsenic trioxide (Ohnishi et al., 2000).

Adverse effect	CTX	MTX	ADR	DNR	EPI	IDA	NOV	AMS
Cardiomyopathy			+++	+++	++	++	++	+
Myo/pericarditis	++		+	++	+			
ECG changes	++	+	++	++				+

CTX, cyclophosphamide; MTX, methotrexate; ADR, doxorubicin; DNR, daunorubicin; EPI, epirubicin; IDA, idarubicin; NOV, mitoxantrone; AMS, amsacrine.

+, rare or little clinical significance; ++, occasional or clinically relevant; +++, common or severe.

Table 1. Main cardiac toxicity for chemotherapy drugs used in acute leukemia

### 3. Hepatotoxicity

Hepatotoxicity is defined as an injury to the liver that is associated with impaired liver function caused by exposure to a drug. The clinical patterns of liver injury are defined as *hepatocellular*, with a predominant initial elevation of the alanine aminotransferase level

(ALT), *cholestatic*, in which the serum alkaline phosphatase concentrations are increased, or *mixed*, if both enzymes are elevated. An ALT level of more than three times the upper limit of normal values and a total bilirubin concentration of more than twice the upper limit are used to define clinically significant abnormalities on liver test. Elevation in serum enzyme levels is taken as indicator of liver injury, whereas increases in bilirubin levels, albumin concentration and the prothrombin time are measures of overall liver function (Navarro & Senior, 2006).

Chemotherapy-induced hepatotoxicity is a common cause of abnormal liver function test in patients with AL. It mainly occurs in an idiosyncratic manner and is generally reversible and nonfatal. This toxicity is manifested in a variety of patterns. In addition to those mentioned above, we find steatosis, ductal injury fibrosis, cirrhosis, veno-occlusion, peliosis hepatis, and nodular regenerative hyperplasia. The two latter lesions appear as pseudometastatic hepatic nodules that may indicate disease progression, especially if they are multiple (Brisse et al., 2000).

Hepatotoxicity usually begins with vague clinical symptoms such as fatigue, anorexia, nausea, dark urine, right upper quadrant discomfort and jaundice. Suspected drug exposure must precede the symptoms and liver injury may improve when administration is stopped. However, the latent period is highly variable and enzyme levels may take weeks to increase. Before attributing these symptoms to a chemotherapy drug, other causes of liver injury must be ruled out (Navarro & Senior, 2006). Abnormal liver function may be due to multiple causes in patients with AL. Leukemic infiltration usually causes mild to moderate hepatomegaly with limited impact on serum transaminase levels. Transfusions increase the likelihood of viral hepatitis. Other circumstances such as sepsis, hypotension or malnutrition may contribute to liver damage (Pihan, 2009).

AL patients are treated with combination chemotherapy, making it difficult to identify the precise agent involved in the hepatic injury. Moreover, diagnosis becomes more challenging by the large number of non-chemotherapeutic drugs commonly used in those patients, some of them holding the potential of being hepatotoxic, e.g. allopurinol, ondansetron and different antifungal agents (Perry, 1992).

Pre-existing liver disease can alter the metabolism and excretion of chemotherapy causing increased and persistent drug levels and hence systemic toxicity. On the other hand, chemotherapy may worsen liver disease, such as occurs with hepatitis. Severe liver dysfunction and fatal fulminant hepatitis through virus reactivation have been described in patients with viral hepatitis. Prophylactic therapy with nucleoside analogues, typically lamivudine, has been recommended for HBs Ag positive patients. This strategy has been reported to allow optimal administration of chemotherapy (Parrish et al., 2010).

### **3.1 Dose modification of chemotherapy with altered hepatic function**

All patients with AL must undergo evaluation of baseline values before starting chemotherapy. This includes liver function test, viral hepatitis serology and, if clinically indicated, hepatic imaging. Liver function test should be reassessed before each course of therapy and known hepatotoxins should be avoided (Perry, 1992). Patients more susceptible to hepatotoxicity such as those with malnutrition or alcoholism, elderly, obese, or diabetic, should be followed up more closely. Liver response may also be abnormal in cases of previous liver disease or coexisting illnesses (Floyd et al., 2006). In cases of elevated liver test (ELT), drugs undergoing hepatic metabolism should be avoided if possible and/or dose



modifications should be considered if guidelines are available. In rare instances in which ELT is caused by leukemic infiltration it is not necessary to adjust dosing (Figure 1).

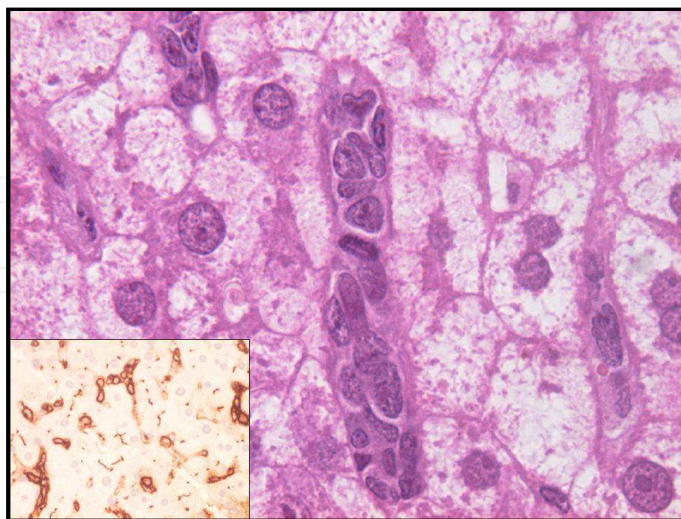


Fig. 1. Liver biopsy of a child with relapsed ALL. Lymphoblasts (C43+) infiltrate the hepatic sinusoids. Despite of abnormal liver test, chemotherapy was administered without complications.

### 3.2 Hepatotoxicity of major chemotherapy agents used in acute leukemia

#### 3.2.1 6-Mercaptopurine and 6-Thioguanine

6-Mercaptopurine (6-MP) in orally daily regimen associated with weekly MTX is the backbone of maintenance chemotherapy acute lymphoblastic leukemia (ALL). Hepatotoxicity produced by this drug include both cholestatic and hepatocellular disease. Characteristic diagnostic profiles include prominently elevated serum bilirubin, typically between 3 and 7 mg/dL, accompanied by mild to moderate elevations in aminotransferases and alkaline phosphatase (Floyd et al., 2006). Liver function tests are transiently abnormal in the majority of children during maintenance of ALL, in the absence of other evidence of severe liver toxicity or viral hepatitis, it is generally not necessary to withhold or reduce the dose of continuation chemotherapy (Pui & Evans, 2006). When liver biopsies are performed in this population, inflammatory and fatty changes are common and not related with ALT levels. Early portal fibrosis is found only in patients with prolonged therapy. The risk of portal fibrosis is low after 2-3 years of continuing chemotherapy and most patients go back to normal ALT values with drug cessation. The mechanism underlying 6-MP-induced hepatotoxicity is related to its methylated metabolites and correlates with ALT levels. Indeed, ALT levels have been proposed as a surrogate marker for treatment compliance (Nygaard et al., 2004). A study by Schmiegelow et al. has shown that ALL pediatric patients with mean ALT levels above the upper normal limit (40 IU/l) who were kept on therapy had a significantly lower risk of hematological relapse compared to other children (Schmiegelow, 1991). These data support the concept of *treating to toxicity* for maintenance therapy.

6-Thioguanine as maintenance treatment in childhood ALL has also been shown to cause hepatic veno-occlusive disease (VOD) usually mild and reversible on withdrawing 6-TG or replacing it with 6-MP (Stoneham et al., 2003).

### 3.2.2 Methotrexate

MTX inhibits dihydrofolate reductase resulting in depletion of critical reduced folates. The net result is effective inhibition of DNA and RNA synthesis and potent cytotoxicity to rapidly dividing cells. MTX causes hepatotoxicity, fibrosis and cirrhosis, but usually after prolonged use and/or when it is used in the treatment of autoimmune diseases.

In a high percentage of patients with ALL, MTX causes isolated elevations of ALT during maintenance chemotherapy, usually transient and asymptomatic. These ALT elevations are not predictive of subsequent hepatic disease and do not require treatment modification (Farrow et al., 1997).

As in the maintenance treatment, when MTX is used in high IV doses (HD-IV MTX), the characteristic hepatotoxic pattern is transient, ALT levels are related to the dose of MTX and increase with the number of cycles received. A difference with the maintenance treatment is that in cases of altered hepatic function it is necessary to modify or suspend the administration of HD-IV MTX (Table 2). In any case, despite the usual benign character of MTX-induced hepatotoxicity, there are reports of hepatoma in association with hepatic fibrosis occurring in children following ALL treatment (Fried et al., 1987).

### 3.2.3 Cytarabine

Cytarabine (ara-C) have revealed a cumulative dose-dependent hepatotoxicity. Several case reports have demonstrated direct histologic evidence of a hepatotoxic role for ara-C, expressed as increased ALT levels or as intrahepatic cholestasis. Although the actual incidence of this toxicity remains to be elucidated, mild elevations of liver function in a cholestatic pattern represent the reversible, rarely fatal clinical picture (George et al., 1984). Ara-C is reported to be partially detoxified in the liver. Therefore, it is recommended that its dose be reduced in patients with liver impairment (Table 2).

### 3.2.4 L-Asparaginase

In addition to hypersensitivity reactions, the most common toxic effects of L-asparaginase are related to the depletion of proteins synthesized in the liver, such as clotting factor, insulin, albumin, haptoglobin and transferrin. Liver function abnormalities (including hyperbilirubinemia and elevated transaminase levels) and hyperlipidemia (hypertriglyceridemia and hypercholesterolemia) have been frequently reported in patients receiving the drug (Earl, 2009). As a result of these metabolic abnormalities, up to 7% of children with AL develop pancreatitis (Treepongkaruna et al., 2009). Another common metabolic complication of this drug is hyperglycemia, which occurs in up to 10% of children with AL during their induction therapy (Pui et al., 1981) and is associated with the synergistic effect of L-asparaginase and glucocorticoids (Spinola-Castro et al., 2009). It should be noted that the use of pegylated asparaginase does not prevent these complications (Silverman et al.).

### 3.2.5 Other drugs

In spite of requiring metabolic activation in the liver, cyclophosphamide, antitumor antibiotics and vinca alkaloids are uncommon hepatic toxins. Indeed, reports of severe hepatotoxicity attributed to these drugs are scarce (Floyd et al., 2006). However, dose modifications are necessary to prevent systemic toxicity in case of liver impairment (Table 2).

Agent	Bilirubin (mg/dl)	Aminotransferases	% Dose administered
<b>Alkylating agents</b>			
Cyclophosphamide	3.1-5	>3 x ULN	75
	>5		0
<b>Antimetabolites</b>			
Cytarabine		Any	50%; increase by monitoring toxicity
6-mercaptopurine			No dose reduction is necessary
Methotrexate	3.1-5.0	>3 x ULN	75
	>5.0		0
6-Thioguanine	>5.0		0
<b>Antibiotics</b>			
Doxorubicin		2-3 x ULN	75
	1.2-3.0	>3 x ULN	50
	3.1-5.0		25
	>5.0		0
Daunorubicin	1.2-3.0		75
	3.1-5.0		50
	>5.0		0
Epirubicin	1.2-3	2-4 x ULN	75
	>3	>4 xULN	50
Idarubicin	1.5-3.0	AST 2-3 x ULN	75
	3.1-5.0	AST>3 x ULN	50
	>5		0
Mitoxantrone	>3.0		75
<b>Plant alkaloids</b>			
Vincristine and Vinblastine*	1.5-3.0	2-3 x ULN	50
	>3.1	>3 x ULN	0
Etoposide	1.5-3.0	AST>3 x ULN	50
	>3	AST>3 x ULN	0
Teniposide			Evaluate if necessary
<b>Miscellaneous</b>			
L-asparaginase			No dose reduction is necessary

\*Vincristine and vinblastine: 50% reduction if alkaline phosphatase is elevated. ULN, Upper limit of normal.

Table 2. Dosage of main chemotherapeutic agents used in AL according to liver function

#### 4. Peripheral neuropathy

The most prevalent neurologic complication of cancer treatment is chemotherapy-induced peripheral neuropathy (CIPN). Vincristine is the main etiological agent involved in peripheral neuropathy in leukemia patients (Kannarkat et al., 2007). Virtually all ALL patients receiving vincristine have some degree of neuropathy. Neurotoxicity commonly presents as peripheral neuropathy, which is predominantly sensory in nature. The clinical manifestations are subjective and predominantly manifest as distal and symmetrically distributed pure sensory symptoms such as paresthesias, hyperesthesias, hypoesthesias, and



dysesthesias. The most common and earliest symptoms are numbness and tingling in the fingertips and feet as well as constipation due to autonomic neuropathy. Symptoms of motor weakness are observed in patients with more persistent and severe sensory findings. Isolated motor weakness with the complete absence of sensory involvement has not been reported. If such findings were observed, consideration should be given to other conditions such as steroid myopathy or diabetic neuropathy (Hausheer et al., 2006).

Sensory findings, as diminished or absent proprioception and vibration are typically diminished in the stocking-glove distribution in symptomatic patients. Loss of ankle stretch reflexes is an early and almost universal sign, and with continued therapy all reflexes may diminish or disappear. The toxicity of vincristine is believed to occur through disruption of microtubule polymerization. Neurophysiologic studies are compatible with a primarily axonal neuropathy. Symptoms develop gradually and may manifest after the first dose. As the disease progresses, muscle weakness becomes apparent, patients lose the ability to walk on their heels and lose strength in wrist extensors. Motor weakness from vincristine can become severe enough to render the patient immobile. In addition, some patients may develop impotence, postural hypotension, or an atonic bladder (Quasthoff & Hartung, 2002). When symptoms are severe, a hereditary motor and sensory neuropathy should be suspected (Mercuri et al., 1999).

Because there is no effective treatment, prevention is the only useful measure for neurotoxicity. All patients should take prophylactic stool softeners and/or laxatives. Dose level and cumulative dose are the most significant risk factors. The maximum dose of 2 mg, and cumulative doses over 15-20 mg should not be exceeded due to the considerable increase in the incidence and severity of symptoms. When symptoms of neuropathy disturb the patient a common practice is to administer vinblastine instead and even to discontinue therapy if marked weakness appears. Recovery generally occurs 1 to 3 months after treatment cessation, withholding the drug or reducing its dose, but CIPN symptoms may also persist or worsen following vincristine discontinuation (Verstappen et al., 2005).

## 5. Central neurotoxicity

Chemotherapy-induced central neurotoxicity can result in multiple clinical manifestations: impaired consciousness, focal deficits, seizures, headaches, etc. However, before attributing these symptoms to chemotherapy in AL patients, other causes must be ruled out first (Table 3). Furthermore, it is necessary to consider other factors such as drug-drug interactions. For instance, MTX intracellular levels may be elevated in the presence of vincristine. In addition, circumstances such as cranial irradiation or CNS affection by leukemia may cause direct damage to the blood-brain barrier, thereby increasing MTX permeability and subsequent toxicity (Naing et al., 2005).

Metabolic disturbances (e.g. hyponatremia)
Intracerebral hemorrhage
Cerebral infarction or venous sinus thrombosis
CNS infection
Meningeal Leukemia
Epilepsy
Migraine
Drugs

Table 3. Main causes of CNS disease in patients with AL

### 5.1 Cerebrovascular accidents

In patients with AL, ischemic or hemorrhagic cerebrovascular accidents may be either a consequence of the disease or a complication of chemotherapy. Intracranial hemorrhage (ICH), which is the second leading cause of mortality in patients with acute myeloid leukemia (AML) (accounting for up to 70% in some series), occurs mostly during induction therapy. Brainstem, epidural and subarachnoid hemorrhage are particularly dangerous (Chen et al., 2009). In a risk score model for fatal intracranial hemorrhage, female gender, thrombocytopenia, prolonged prothrombin time, hyperleukocytosis (particularly in presence of symptoms of pulmonary leukostasis), and acute promyelocytic leukemia (APL), were significantly associated with the occurrence of this complication (Kim et al., 2006).

Thrombotic events, particularly sino-venous thrombosis, are more frequent in ALL. Therapy with L-asparaginase is considered the major risk factor for this complication in these patients. Thrombosis develops after the administration of the first doses of the drug in induction therapy. The most common symptoms are headaches and seizures which resolve without sequelae in most cases (Kieslich et al., 2003). In a previous study with 238 patients treated with L-asparaginase, 4.2% of patients showed cerebral thrombosis and 2.1% cerebral haemorrhages (Nicholson et al., 1996). In this regard, it has been shown that increased triglycerides and decreases of antithrombin III, fibrinogen, protein S, protein C, plasminogen and alpha-2-antiplasmin are associated with the dose of L-asparaginase (Hongo et al., 2002; Nowak-Göttl et al., 1994). Other factors such as central venous catheters, obesity, use of steroids and thrombophilia may contribute to thrombotic imbalance in these patients.

### 5.2 Aseptic meningitis

Aseptic meningitis or chemical arachnoiditis is the most common neurotoxicity induced by MTX. It affects approximately 10% of patients receiving intrathecal (IT) therapy. The onset is generally abrupt and occurs within hours of IT administration. The patient has headache, meningismus, nausea, vomiting, fever, and altered consciousness. Cerebrospinal fluid (CSF) studies demonstrate pleocytosis and elevated protein. The symptoms are self-limited and usually resolve within 72 hours. Further treatment with IT MTX is not contraindicated and patients may receive subsequent doses of chemotherapy without incident. Co-administration of MTX and IT hydrocortisone or premedication with oral corticosteroids may be useful to prevent the syndrome (Sul & Deangelis, 2006). The use of IT ara-C can also result in aseptic meningitis similar to that seen with IT MTX. The incidence has been observed to be higher with the liposomal formulation (DepoCyt®), which maintains cytotoxic concentrations of the drug in the CSF for up to 14 days. Side effects become so frequent that all patients require prophylactic corticosteroids pre and post DepoCyt® administration (Glantz et al., 1999).

### 5.3 Transverse myelopathy

Transverse myelopathy is an uncommon complication of IT MTX manifested by the development of back or leg pain followed by paraplegia, sensory loss, and sphincter dysfunction in the absence of a compressive lesion. The onset is usually between 30 minutes and 48 hours after treatment, although the reaction may also appear up to two weeks later. MRI may illustrate cord edema and irregular post-gadolinium enhancement. In contrast to myelopathies caused by other reasons, corticosteroids are not helpful. This is thought to be

an idiosyncratic drug reaction, and therefore the identification of potentially susceptible patients is not possible. Unlike aseptic meningitis, transverse myelopathy is an absolute contraindication to further treatment with IT MTX. In addition to IT MTX, a similar transverse myelopathy was reported in two pediatric AML patients receiving IT and IV ara-C (Sul & Deangelis, 2006).

#### **5.4 Acute encephalopathy**

High doses of Cytarabine (HD-ara-C) ( $\geq 3$  g/m<sup>2</sup> every 12 hours) may result in CNS dysfunction, especially impaired cerebellar function. The characteristic syndrome begins with somnolence and occasionally encephalopathy that develops two to five days after treatment. Immediately thereafter, cerebellar signs are noted on physical examination. Symptoms range in severity from mild ataxia to inability to sit or walk unassisted. Rarely, seizures may also develop. There may be MRI changes in the white matter and cerebellum, but the CSF is usually normal. Discontinuation of therapy generally results in partial recovery within several weeks, but complete resolution is achieved by only 30% of patients. Neurologic deficits can be permanent if treatment is continued after the onset of symptoms (Friedman & Shetty, 2001).

Since the occurrence of severe cerebellar dysfunction is greatly affected by age, patients older than 50 years should be given a reduced schedule of HD-ara-C. Furthermore, it has been shown that avoidance of very high doses of the drug in patients with renal impairment and the administration of HD-ara-C on a once-daily rather than twice-daily schedule reduce the incidence of this syndrome (Smith et al., 1997).

#### **5.5 Subacute encephalopathy**

Subacute encephalopathy is an uncommon complication of MTX therapy that generally develops within 5–14 days after the administration of IT or HD-MTX, not being observed in maintenance therapy when low doses of oral or parenteral MTX are used. The syndrome is manifest by abrupt onset of focal neurological deficits, such as aphasia or hemiparesis and presents after a median of three courses of IV or IT MTX. Typical symptoms are headache and nausea followed by stroke-like hemiparesis or bilateral weakness. Hemiparesis may be alternating and evolving over a period of minutes to hours. In addition, aphasia or expressive dysphasia, emotional lability and disorientation are also common signs. Other manifestations such as seizure, transient ataxia, choreoathetoid movements, temporary blindness or visual hallucinations are less frequent. Most neurological symptoms resolve after 1–7 days and the majority of patients can resume HD-MTX therapy without permanent neurological sequelae. Recurrence may be experienced by 10–56% patients (Inaba et al., 2008).

In the absence of histopathological data, diagnosis is based upon spinal fluid analysis and neuroimaging techniques. CSF analysis is usually normal and electroencephalogram (EEG) shows nonspecific diffuse or focal slowing. At the onset of MTX-induced encephalopathy, conventional CT scans, T1 or T2 weighted MR imaging and angiography typically show no abnormalities, whereas diffusion-weighted imaging (DWI) is able to show restricted diffusion of water in the brain that clears after resolution of the clinical symptoms. These abnormalities are consistent with cytotoxic or intramyelinic sheath edema within white matter tracts (Haykin et al., 2006). Follow-up MR imaging shows variable abnormal T2 and FLAIR signal intensity in the deep white matter, with no detectable neurological sequelae in most patients (Haykin et al., 2006) (Figure 2). The pathogenesis of MTX neurotoxicity is

poorly understood and no specific risk factors for the development of this complication have been identified to date. Indeed, pharmacokinetic data are normal in most patients with MTX-induced neurotoxicity (Rubnitz et al., 1998). In this regard, there are recent data indicating that pharmacogenetics could play a significant role in the development of this complication (Mahadeo et al., 2010; Vagace et al., 2011).

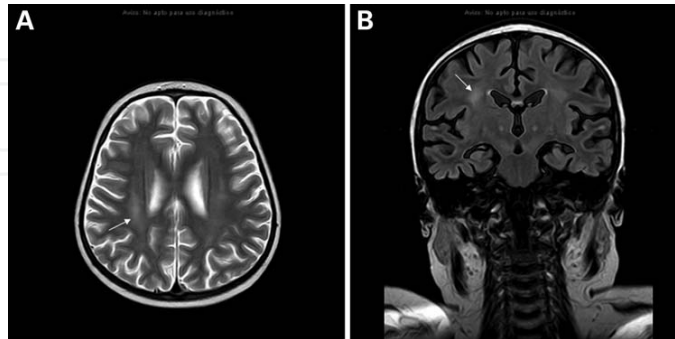


Fig. 2. MR imaging findings six weeks after an episode of subacute encephalopathy by MTX. White arrows in Axial T2 (A) and coronal FLAIR (B) sequences show deep and periventricular white matter hyperintensity, especially in the right hemisphere (Vagace et al., 2011).

### 5.6 Posterior reversible encephalopathy

In 1996, Hinchey et al. described a reversible syndrome of headache, altered mental functioning, seizures, and loss of vision associated with abnormalities on neuroimaging in the posterior regions of the cerebral hemispheres. The syndrome occurred in patients who had renal insufficiency or hypertension or in those who were immunosuppressed. Although not previously recognized as a complication of chemotherapy, *Posterior Reversible Encephalopathy* (PRE) is now considered as one of the most common abnormalities leading to seizures in children with leukemia (Norman et al., 2007). The patient usually presents with headache, altered alertness, confusion, seizures (that may begin focally but usually become generalized), vomiting and alterations of visual perception. These visual disturbances are nearly always detectable with symptoms such as blurred vision, hemianopia, visual hallucinations or cortical blindness. Hypertension and hypomagnesemia are additional diagnostic criteria but are not always present (Dicuonzo et al., 2009).

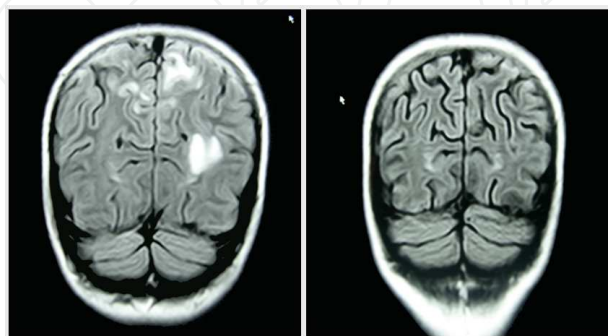


Fig. 3. *Posterior Reversible Encephalopathy*: MR imaging, Coronal T2 FLAIR, of a child with AL treated with vincristine that developed headache, hypertension and seizures. Left panel shows white matter hyperintensity in both hemispheres. After 18 days (right panel) these signs were inappreciable.



The cardinal features of PRE are both clinical and radiologic. Abnormalities are usually observed in bilateral, parietal and occipital lobes. CT scans typically show posterior cerebral white-matter hypodensities. If PRE is suspected, MRI series should be performed, including T2, DWI, and FLAIR images for the most accurate diagnosis. MR abnormalities are characterized by increased signal on T2-weighted and FLAIR sequences. DWI may appear normal or show increased diffusion consistent with vasogenic edema (Shin et al., 2001) (Fig 3). Sudden elevations in systemic blood pressure exceeding the autoregulatory capability of the brain vasculature, leading to capillary leakage and subsequent vasogenic edema has been proposed as the underlying mechanism of PRE. The preferential involvement of the parietal and occipital lobes may be due to the observed relative reduction in the sympathetic innervation of the posterior circulation. Based on brain SPECT studies, a migraine-like mechanism has been proposed by other authors. Additionally, hypomagnesemia or vascular instability resulting from the toxicity of the chemotherapy agents on the endothelium of the blood-brain barrier may also be contributing factors (Sanchez-Carpintero et al., 2001). Most cases of PRE occur during induction chemotherapy for ALL, consequently, a variety of drugs routinely used during this phase have been linked to PRE, namely vincristine, IT MTX, HD-MTX, L-asparaginase, cyclophosphamide and ara-C (Gupta et al., 2008). Early and aggressive therapy for hypertension and quickly control the seizures, are the only defined treatment recommendations for this syndrome. In most patients chemotherapy can be restarted without recurrence or permanent neurological sequelae. In conclusion, chemotherapy for AL should be added to the growing list of causes of PRE. However, more information is needed before a clear association can be established between PRE and specific chemotherapy agents (Titos-Arcos et al., 2011).

### **5.7 Chronic Leukoencephalopathy**

Chronic leukoencephalopathy is a commonly described but poorly understood phenomenon, which is associated with the use of HD-MTX with inadequate leucovorin rescue and that may be exacerbated by prior cranial irradiation. This complication presents several months to years after therapy and may lead to severe neuropsychological impairment (Ziereisen et al., 2006).

## **6. Renal toxicity and electrolytes imbalance**

The kidneys, being the elimination pathway of many antitumor drugs and their metabolites, are quite vulnerable to injury in chemotherapy. Several factors are known to contribute to the nephrotoxic potential of antineoplastic drugs in patients with AL, namely the concomitant use of other nephrotoxic drugs (e.g., amphotericin), urinary infections, intravascular volume depletion, sepsis and other comorbidities such as hypertension, diabetes mellitus or heart failure. Suggested dosing of the main chemotherapeutic drugs used in AL according to renal function is shown in Table 4.

Chemotherapy-induced nephrotoxicity may affect glomeruli, tubules, renal vasculature or excretory system depending on the drugs involved. Creatinine clearance is the usual measure to assess the glomerular filtration rate. Serum creatinine is less sensitive for this purpose and does not significantly change until the clearance is below 70 ml/min. Measurement of the tubular function is often accomplished by evaluating the fractional excretion of glucose, uric acid, calcium, phosphorous and magnesium (de Jonge & Verweij, 2006).



### 6.1 Hemorrhagic cystitis

Cyclophosphamide and ifosfamide are drugs with similar chemical structures that are biotransformed to acrolein. Hemorrhagic cystitis occurs subsequent to urinary excretion of this metabolite, which is capable of binding the sulfhydryl constituent within proteins of bladder epithelium causing an inflammatory process. Saline-based hyperhydration and mesna (2-mercaptoethane sulfonate), which binds acrolein preventing direct contact with the uroepithelium, are concurrently administered to reduce the incidence and severity of hemorrhagic cystitis. Hemorrhagic cystitis is usually seen in transplant recipients who are treated with doses of cyclophosphamide higher than those used in AL. When the process lasts longer than 7 days, adenovirus and polyomavirus infection (specifically BK viruria) are often responsible (Korkmaz et al., 2007).

Treatment of hemorrhagic cystitis is challenging. If blood clots form, bladder irrigation with isotonic saline may be required to break up an obstructive uropathy. Other measures that have been used include intravesical therapy with instillation of chemicals to cause mucosal fibrosis, hyperbaric oxygen therapy, and embolization or ligation of internal iliac arteries. Cystectomy is reserved for massive bladder hemorrhage, a clinical problem with a high mortality rate (Hu et al., 2008).

Agent	CrCl (ml/min)	[Cr]s (mg/dl)	% Dose administered
Alkylating agents			
Cyclophosphamide	10-50		75
	<10		50
Antimetabolites			
Cytarabine			Evaluate if necessary
6-mercaptopurine			No formal recommendation.
Methotrexate	30-60		50
	<30		0
Antibiotics*			
Daunorubicin		>3.0	50
Plant alkaloids			
Etoposide	10-50		75
	<10		50
Miscellaneous			
L-asparaginase	<60		0

CrCl, creatinine clearance; [Cr]s, serum creatinine

\*No reduction is necessary for mitoxantrone, doxorubicin, epirubicin, idarubicin, vincristine or vinblastine

Table 4. Dosage of main chemotherapeutic agents used in AL according to renal function

### 6.2 Methotrexate-induced nephrotoxicity

Nephrotoxicity is a potentially life-threatening complication of HD-MTX therapy (>1g/m<sup>2</sup>). Both the parent drug and the 7-hydroxy-MTX metabolite may precipitate in the acidic environment of renal tubules and collecting ducts producing acute tubular necrosis. Renal dysfunction results in delayed MTX excretion and sustained elevated plasma MTX

concentrations, which in turn may lead to a marked enhancement of other toxicities of MTX, especially myelosuppression, mucositis, hepatitis, and dermatitis. Uniform institution of aggressive hydration, alkalinization (urinary pH monitoring required), and pharmacokinetically guided leucovorin rescue, significantly reduce the morbidity rate in patients receiving this therapy. Implementation of this regimen reduces the incidence of nephrotoxicity to approximately 2% of patients (Widemann & Adamson, 2006).

Delayed MTX excretion and high plasma MTX concentrations identify patients at high risk of toxicity. These subjects may benefit from supplemental leucovorin rescue or from the administration of glucarpidase (carboxypeptidase G2, CPDG2), a recombinant enzyme with cleaves MTX in inactive metabolites and is able to lower plasma MTX concentrations rapidly and efficiently. The use of CPDG2 is well-tolerated and renders a more profound, rapid, and consistent decrease in plasma MTX concentrations compared to dialysis-based methods, and should therefore be considered over dialysis in patients with HD-MTX-induced renal dysfunction (Patterson & Lee, 2010).

### 6.3 Syndrome of inappropriate antidiuretic hormone secretion

Hyponatremia is the most common electrolyte disorder in clinical medicine and occurs in approximately one of every three hospitalized patients. The *syndrome of inappropriate Secretion of Antidiuretic Hormone* (SIADH) is the most frequent cause of hyponatremia. Malignant diseases, pulmonary and CNS disorders and drugs are causes of SIADH. With regard to chemotherapy drugs used in AL, vincristine and cyclophosphamide have been implicated in this complication (Ellison & Berl, 2007).

The diagnosis of SIADH requires the presence of hyponatremia ( $\text{Na}^+ < 135 \text{ mmol/L}$ ) with a low serum osmolality ( $< 275 \text{ mmol/L}$ ) in the absence of other causes of hyponatremia such as oral or IV water excess, low effective circulating volume (heart or liver failure), use of thiazide diuretics, endocrine processes (hypopituitarism, adrenal insufficiency or hypothyroidism), renal failure or salt wasting. On the other hand *Cerebral Salt Wasting* is a syndrome due to the production of natriuretic factor and/or a disruption of neural input into the kidney that decreases proximal sodium reabsorption, resulting in a loss of sodium by the urine. The identification of this disorder is of considerable clinical importance because its treatment comprises vigorous sodium and volume replacement, whereas fluid restriction is the treatment of choice in SIADH (Hoorn & Zietse, 2008). Table 5 shows useful data to differentiate between these two syndromes.

	CSW	SIADH
Extracellular fluid volumen*	Decreased	Increased
Diuresis	Normal or increased	Normal or decreased
Hematocrit	Increased	Normal
Plasma BUN/Creatinine	Increased	Decreased
Treatment	Normal saline	Fluid restriction

\*The main difference but clinical assessment of volume status is imprecise. CSW, cerebral salt wasting; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Table 5. Clinical features of CSW and SIADH [Modified from (Palmer, 2003)].

## 7. Pulmonary toxicity

Most pulmonary complications in AL patients are due to concurrent medical problems, such as bacteremia, sepsis, fungal infection or CHF. These patients also show an increased risk of thromboembolic disorders. Therefore, the occurrence of acute respiratory insufficiency in AL may be suspicious of pulmonary thromboembolism, especially if treatment with L-asparaginase was previously implemented. L-asparaginase reduces antithrombin III levels thereby increasing the risk for thrombosis, which may be safely prevented with the use of heparin (Meister et al., 2008).

Other chemotherapy drugs such as all-trans-retinoic acid (ATRA), imatinib and ara-C can cause a capillary leak syndrome which manifests as pulmonary edema, pleural effusions, pericardial effusions or ascites. Drug withdrawal and steroid therapy is generally recommended in this case (Meadors et al., 2006).

### 7.1 The Acute Promyelocytic Leukemia Differentiation Syndrome

All-trans retinoic acid (ATRA) and arsenic trioxide are agents used for the treatment of the acute promyelocytic leukemia (APL) with a unique toxicity profile. The *APL Differentiation Syndrome* or *Retinoic Acid Syndrome* is mediated by endothelial inflammation and vascular leak that occurs when leukemic blasts suddenly differentiate into mature granulocytes and adhere to pulmonary endothelium. The differentiation syndrome occurs in approximately 25% of patients with APL treated with these agents (Luesink et al., 2009; Montesinos et al., 2009).

Diagnosis should be suspected clinically in the presence of dyspnea, unexplained fever, weight gain, peripheral edema, unexplained hypotension, acute renal failure or CHF, but particularly by a chest radiograph demonstrating interstitial pulmonary infiltrates or pleuro-pericardial effusion. In this situation, dexamethasone should be started promptly and ATRA temporarily discontinued if the patient develops respiratory distress or renal failure. Prophylactic treatment with corticosteroids is recommended in patients with a WBC count greater than  $5 \times 10^9/l$  to reduce mortality and morbidity (Sanz et al., 2009).

## 8. Cutaneous toxicity

Cutaneous side effects related to chemotherapy (Table 6) may range from relatively common adverse events, such as alopecia or hyperpigmentation (which are the result of direct toxicity on skin in contact with the drugs through blood or sweat) to more unusual phenomena such as photosensitivity or hypersensitivity reactions (DeSpain, 1992).

Most chemotherapeutic agents may cause alopecia. Hair loss usually begins 7 to 10 days after the initiation of treatment and is prominent within 1 to 2 months of treatment. Once chemotherapy is finished hair grows back in the majority of the patients, although it may present a different texture or color.

Pigmentary changes involving the skin, nails, and mucous membranes are usually related to alkylating agents and antitumor antibiotics, but they may as well occur with other drugs used in AL, namely etoposide, MTX or vincristine. The latter may cause a distinctive pattern of hyperpigmentation called *Serpentine Hyperpigmentation*, which follows an underlying vein proximal to an infusion site (Payne, A.S. et al., 2006).

*Eccrine Squamous Syringometaplasia* is characterized by self-limited, asymptomatic erythematous papules on trunk and extremities that may be confused with erythema nodosum.

MTX can produce a phototoxic recall reaction (*Photoreactivation*) in the absence of light. It is characterized by an erythematous eruption in the distribution of UV-induced sunburns that

may have occurred months or years prior to the administration of the drug. HD-MTX is also associated with severe erythema in sun-exposed areas when the drug is given within two to five days of exposure to UV light. In contrast to *Photoreactivation*, retreatment with MTX does not usually reproduce the reaction (Payne, A.S., DMF, 2011). Patients receiving photosensitizing drugs should be counseled regarding the risk of adverse reactions to sunlight and encouraged to use UV protection with sunscreens and protective clothing.

Agent	AL	CP	ESS	PS	AE	NEH	SS	HR
Alkylating agents	+							
Cyclophosphamide	+	+	+			+		+
Ifosfamide	+							
Antimetabolites								
Cytarabine	+		+		++	++		+
6-mercaptopurine					+			
Methotrexate	+	+	+	+	+			+
Antibiotics								
Doxorubicin	+		+		+	+		+
Plant alkaloids								
Vincristine and Vinblastine*	+	+		+				
Etoposide	+		+		+			++
Tyrosine kinase inhibitors								
Imatinib		+		+			+	
Miscellaneous								
L-asparaginase								++
Tretinoin (ATRA)							+	

AL, Alopecia; CP, Cutaneous Hyper-Pigmentation; ESS, Eccrine squamous syringometaplasia; PS, Photosensitivity; AE, Acral erythema; NEH, Neutrophilic eccrine hidradenitis ; SS, Sweet's Syndrome; HR, Hypersensitivity reactions.

Table 6. Cutaneous toxicity of the main chemotherapy agents used in AL.

*Acral Erythema or Hand-Foot Syndrome*, is characterized by painful erythematous plaques on the palms and soles and heals with prominent desquamation that usually resolves within two to four weeks after discontinuation of the causative agent (Figure 4).



Fig. 4. Hand-Foot Syndrome in a child treated with ara-C for AL

*Neutrophilic Eccrine Hidradenitis* (NEH) is a reactive disorder that may occur in association with malignancy (with or without chemotherapy), infections, and certain medications. NEH is characterized by asymptomatic and self-limited violaceous plaques on the trunk and extremities. In all cases of suspected NEH, a biopsy should be performed to differentiate of septic emboli, metastatic infiltrates or *Sweet's Syndrome* (Brehler et al., 1997).

*Sweet's Syndrome* (SS), also called *Acute Febrile Neutrophilic Dermatitis*, is characterized by fever, neutrophilia, erythematous and painful skin lesions, diffuse neutrophilic infiltrate in the dermis, and rapid response to corticosteroids (Saavedra et al., 2006). Ten to twenty per cent of SS cases are related to neoplasms, especially AML, the remaining being idiopathic or drug related. In AL patients, therapy with cytokines such as granulocyte colony-stimulating factor (G-CSF) and all-trans retinoic acid (ATRA) are involved in most cases (Thompson & Montarella, 2007) (Figure 5).



Fig. 5. *Sweet Syndrome* in an adult patient treated with ATRA for APL

Hypersensitivity reactions (HR) typically occur within an hour of drug administration and are characterized by pruritus, urticaria, swelling at the injection site, rash and in more severe cases, bronchospasm and hypotension. L-Asparaginase shows the highest risk for such reactions. The overall risk approaches 30% after four doses, but it can be also observed after the first dose. Some risk factors for this reaction are IV administration, prior exposure to L-Asparaginase and weekly intervals of administration (as opposed to daily).

There is no reliable method for determining who will sustain a HR with this drug. Skin testing is not worthwhile for this purpose. Changing to intramuscular *Erwinia* L-asparaginase instead of *E.Coli* L-asparaginase or use modified asparaginase with attached polyethylene glycol are suitable options for sensitized patients (Earl, 2009). Etoposide is also capable of producing HR in 6-7% of patients from the first dose, especially when the drug is infused. Recommended anaphylaxis precautions for patients receiving these drugs include: blood pressure monitoring, premedication with IV diphenhydramine and having an IV access to administer epinephrine and corticosteroids in case of reaction (Shepherd, 2003).

Ara-C causes an acute reaction called the *Cytarabine Syndrome* characterized by high fever, rigors, diaphoresis, myalgia, arthralgia, conjunctivitis and maculopapular rash. This ara-C syndrome may not be a HR but a constellation of direct toxicities of the drug which is likely mediated by cytokines. Corticosteroids are the treatment of choice for this syndrome (Chng, 2003).



## 9. Pharmacogenetics determinants of chemotherapy toxicity in Acute Leukemia

The fact that the efficacy of chemotherapy in AL patients has significantly increased in the last twenty years, has rendered a growing body of pharmacogenetic studies focused on toxicity rather than efficiency of chemotherapy drugs. Indeed, some genetic polymorphisms have been identified to play an important role.

Most notably, polymorphisms in the thiopurine methyltransferase (*TPMT*) gene, which codes for a key enzyme in the metabolism of 6-MP, have been shown to produce a defective enzyme. Individuals homozygous for these SNPs present extremely high levels of active thioguanine nucleotides and therefore may have unacceptable, life-threatening toxicity from normal doses of 6-MP. In consequence, AL patients scheduled to receive 6-MP are regularly tested for polymorphisms in the *TPMT* gene in order to adjust therapy (Relling et al., 1999).

MTX, the cornerstone for therapy of ALL, has also been the focus of many pharmacogenetic studies aimed to identify genetic determinants of its toxicity. The methylenetetrahydrofolate reductase (*MTHFR*) gene has been by far the most extensively studied. Two polymorphisms, C677T and A1298C, have been associated with increased MTX toxicity, with the first likely playing a more significant role (Gervasini, 2009). Accordingly, some ALL treatment protocols in the induction phase include MTX dose reductions for subjects homozygous for the 677T variant or for those carrying both heterozygous genotypes (Badell et al., 2008). Given the complexity of the MTX mechanism of action, there are possibly polymorphisms in genes other than *MTHFR* that could be involved in the development of MTX adverse effects. Particularly, the occurrence of polymorphisms in membrane transporters that are responsible for the intake and efflux of MTX may constitute an exciting field of research (Gervasini, 2009).

There are other drugs included in the chemotherapy of AL whose toxicity may also be increased by the presence of genetic polymorphisms. In this regard, some studies have addressed the impact of polymorphisms in ATP binding cassette (ABC) transporters on the toxicity of imatinib, vincristine or mitoxantrone, albeit with contradictory results (Cotte et al., 2009; Gurney et al., 2007; Hartman et al., 2010; Plasschaert et al., 2004). In addition, polymorphisms in drug-metabolizing enzymes such cytochrome P450 (CYP) 2B6 or CYP2D6 may also be involved in the occurrence of adverse effects in response to treatments including imatinib, cyclophosphamide and etoposide (Gardner et al., 2006; Kishi et al., 2004; Rocha et al., 2009). However, these results are far from being consistently demonstrated and further studies are needed to elucidate whether these polymorphisms represent a clinical concern.

## 10. Conclusions

In this chapter we have aimed to describe a number of guidelines to correctly recognize and treat the main adverse effects induced by chemotherapy in AL patients. In order to identify subjects at higher risk of toxicity, a complete clinical-analytical evaluation must be performed in all patients before the administration of each chemotherapy cycle. Furthermore, clinicians should be familiar with the different metabolic pathways of each administered drug, and doses should be adjusted accordingly if necessary, especially in cases with decreased renal or liver function. However, even with these precautions, chemotherapy-induced toxicity is still

an important clinical concern in AL. Indeed, at the present time the cornerstone of therapy for AL is still formed by a reduced number of drugs with a highly toxic profile.

The present challenge would therefore be to reduce the frequency and seriousness of adverse effects while maintaining efficacy and avoiding overtreatment of patients. The design of new drugs such as the so-called molecular target drugs, the further development of existing therapeutic groups, or the knowledge of genetic determinants of toxicity may help achieve these goals.

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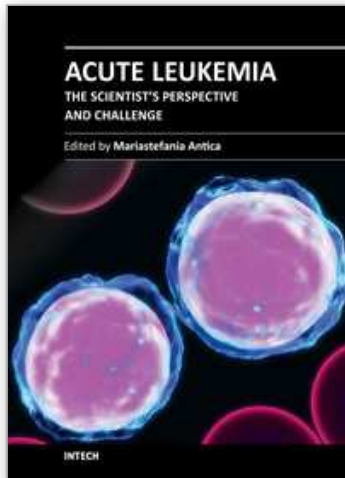


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## **Acute Leukemia - The Scientist's Perspective and Challenge**

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This book provides a comprehensive overview of the basic mechanisms underlying areas of acute leukemia, current advances, and future directions in management of this disease. The first section discusses the classification of acute leukemia, taking into account diagnoses dependent on techniques that are essential, and thankfully readily available, in the laboratory. The second section concerns recent advances in molecular biology, markers, receptors, and signaling molecules responsible for disease progression, diagnostics based on biochips and other molecular genetic analysis. These advances provide clinicians with important understanding and improved decision making towards the most suitable therapy for acute leukemia. Biochemical, structural, and genetic studies may bring a new era of epigenetic based drugs along with additional molecular targets that will form the basis for novel treatment strategies. Later in the book, pediatric acute leukemia is covered, emphasizing that children are not small adults when it comes to drug development. The last section is a collection of chapters about treatment, as chemotherapy-induced toxicity is still a significant clinical concern. The present challenge lies in reducing the frequency and seriousness of adverse effects while maintaining efficacy and avoiding over-treatment of patients.

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