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Acute Lymphoblastic Leukemia: What Have We Learned About the Effects of This Disease and Its Treatment on the Nervous System?

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1. Introduction

The treatment of leukemia remains the success story of cancer. The patients with acute lymphoblastic leukemia survive longer and longer, with the rates of long time remission of over 80% in children and 30-40% in adults. Therefore, increased attention is given to diagnose and prevent central nervous system (CNS) complications, not only in order to increase the survival, but also in order to prevent neurologic deterioration and the resulting decreased quality of life.

CNS disease is relatively rare at diagnosis, with less than 10% of the patients being diagnosed with his condition. However, the rate of CNS involvement escalates to up to 75% in the first year, if no effective brain-targeted treatments are used- which justifies the need for CNS prophylaxis even in the absence of frank metastatic involvement.

Classically, patients received cranial radiation. However, a significant percentage of ALL survivors that received cranial radiation now present with a discouraging array of complications, including neurodevelopmental sequelae, strokes, seizures and increased rate of secondary CNS malignancies. More recent, it was suggested that effective CNS prophylaxis can be achieved with a combination of high dose systemic chemotherapy and intrathecal chemotherapy. Though less toxic, some survivors of this approach are still plagued by neurological complications, including cognitive deficits due to the effects of chemotherapy on the developing brain.

More research needs to be conducted on further decreasing the rate on CNS relapse, while minimizing the therapy effects of the brain. Our knowledge of the biological mechanisms involved in radiation and chemotherapy effects of different cerebral structures has to improve. For the ALL survivors, therapies to repair the cognitive damage caused by cancer treatments are still in infancy.

2. CNS Involvement in Acute Lymphoblastic Leukemia (ALL)

2.1 Diagnosis and Incidence

ALL is the most common malignancy in children. It follows a bimodal distribution, with a peak between the ages of 4 and 10, and a second peak after the age of 50 (M.J. Horner, 2009). It accounts for approximately 25% of all childhood cancers occurring in those younger than

20 years of age (Ries et al., 1999). In the United States, there are approximately 3000 cases of childhood ALL diagnosed each year, with an incidence of 3-4 cases per 100,000 children (Jemal et al., 2004). This incidence is similar worldwide. The incidence of ALL varies considerably with age. There is a sharp peak in ALL incidence among children 2-5 years of age, and this trend subsequently decreases with age. The median age at diagnosis is 4 years. Sex differences have been reported with the incidence greater in boys (Smith, et al., 1999). Race differences in incidence have also been observed. African Americans have a much lower incidence of childhood ALL compared to Whites. The incidence of ALL appears to be highest in Hispanic children (Ries et al., 1999).

At presentation, a bone marrow evaluation and lumbar puncture are performed. The bone marrow is the diagnostic test to establish the diagnosis of leukemia and determine the subtype. The lumbar puncture is required for cytologic examination to determine whether there are leukemic cells in the cerebrospinal fluid (CSF) - CNS leukemia. CNS leukemia can occur through several mechanisms. The presence of leukemic cells in the CSF can arise from hematogenous spread of lymphoblasts in the peripheral blood or by direct extension from involved bone marrow into the CSF (Bleyer, 1989; Pinkel & Woo, 1977; Azzarelli & Roessmann, 1977). Bleyer reports that the hematogenous migration through venous endothelium into the CNS is influenced by factors such as lymphoblast count, thrombocytopenia and maturity of the blood-brain barrier. Direct extension occurs by the migration of leukemic cells from the involved skull bone marrow through the choroid plexus into the CSF. The lymphoblasts subsequently invade the cerebral parenchyma or enter the leptomeninges.

Examination of CSF to determine the presence of leukemic cells is an important factor in assigning CNS directed therapy for children with leukemia (Figure 1). The cells are spun in a process called cytocentrifugation which allows for the leukemic cells to be concentrated, increasing the sensitivity of diagnosis of CNS leukemia (Lauer et al., 1989). Table 1 outlines the National Cancer Institute (NCI) derived criteria for grading CNS involvement at diagnosis. CNS 1 status is defined as having no leukemic lymphoblasts in the CSF. CNS 2 is defined as having less than 5 WBC per mL and blasts on CSF cystopin. CNS 3 or overt CNS disease is defined as having more than 5 WBC per mL and CSF lymphoblasts (or with cranial nerve palsy). Approximately 3% of children have overt CNS leukemia (CNS 3) at presentation. Another 15% are CNS 2 status at diagnosis (Mahmoud et al., 1993; Burger et al., 2003). The NCI criteria for grading CNS involvement assumes that the CSF is not contaminated with peripheral blood contents by a traumatic or "bloody tap". However, if a patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥5/mL WBCs (white blood cells) and blasts, many protocols employ the Steinherz/Bleyer algorithm to distinguish between CNS 2 and CNS 3 disease:

CSF WBC/CSF RBC > 2X Blood WBC/Blood RBC

Thus, if the patient has blasts in the peripheral blood and the lumbar puncture is traumatic (containing ≥5/mL WBCs and blasts), CNS disease (CNS 3) is present if the CSF WBC/RBC is is greater than 2 times the blood WBC/RBC. For example, if a patient has a traumatic tap with the following laboratory values: CSF WBC = 70/mL; CSF RBC = 1400/mL; blood WBC = 4300/mL; blood RBC = 3.5 X 10^6/mL:

$$\frac{70}{1400} = 0.05 > 2X \quad \frac{43000}{3.5 \times 10^6} = 0.012$$

In this example, the CSF WBC/RBC is 0.05, which is 2X greater than the blood WBC/RBC of 0.012. Thus, this patient would have CNS 3 status.

A study by Mahmoud, et al. noted specific characteristics in patients who presented at diagnosis with CNS leukemia. They found that patients with CNS leukemia at diagnosis were more likely to be less than one year of age and had a leukocyte count greater than 100 X 10^6/mL, an anterior mediastinal mass, a T-cell phenotype, or blast cells not expressing CD10 antigen (Mahmoud, 1993). Symptoms of CNS leukemia can vary. The majority of children with leukemia in the CSF are asymptomatic. The CSF pressure may be normal with no abnormalities of CSF chemistry. With overt CNS leukemia (CNS 3) or advanced disease, symptomatic patients can present with elevated CSF pressure and symptoms which include headache, vomiting, seizures, and irritability (Laningham et al., 2007). Patients with overt CNS disease can also experience cranial nerve palsies, which typically involve unilateral facial nerve (VII) palsy (Paryani et al., 1983).

Overt CNS leukemia (CNS 3) is present in about 3% of children at initial presentation (Mahmoud et al., 1993; Burger et al., 2003). CNS 3 is considered high risk and associated with a poorer event-free survival (Smith et al., 1996; Pui & Crist, 1994; Hammond et al., 1986). In one study, CNS 3 leukemia at diagnosis was an independent predictor of inferior event free survival (Pui et al., 2009). Approximately 15-20% patients with ALL have CNS 2 status. Controversy exists as to the significance of CNS 2 disease, in which the CSF WBC count is low (less than 5 WBCs per mL) with the presences of CSF blasts. The Children's Cancer Group found that CNS 2 status is of no prognostic significance (Gilchrist et al., 1994; Tubergen et al., 1994). However, other investigators contend that CNS 2 disease was associated with a higher rate of CNS relapse when compared to those with undetectable CSF lymphoblasts (CNS 1) (Mahmoud et al., 1993; Lauer et al., 1994).

2.2 Therapy for ALL

The treatment of childhood ALL begins with risk stratification based on clinical and laboratory features. Risk-based therapy is utilized so that children who have favorable features and more likely to have good outcome are spared the more intensive and potentially toxic therapy reserved for patients who are higher risk, who would otherwise have a poorer outcome without the aggressive treatment. Age and leukocyte count at diagnosis are the most important prognostic factors (Margolin & Poplack, 2006). Hyperleukocytosis is associated with a worse outcome. Approximately 20% of children with ALL have a leukocyte count of > 50 X 10^6/mL, which has been noted to have a poorer prognosis (Margolin & Poplack, 2006). Age at diagnosis also influences outcome: children whose age at diagnosis is < 2 years or older than 10 years have a worse prognosis than those in the intermediate age group (Sather, 1986). In particular, infants with ALL aged < 12 months fared the worst (Kosaka et al., 2004). The identification of cytogenetic abnormalities also has important prognostic implications. In general, for patients with B-cell precursor ALL, favorable cytogenetic prognostic factors include hyperdiploidy (having more than 50 chromosomes per leukemia cells), TEL-AML1 fusion gene, and double trisomies 4 and 10. Cytogenetic prognostic markers which confer a less favorable outcome include hypodiploidy (fewer than 45 chromosomes, t(4;11) with the MLL-Af4 fusion gene which is seen 50% of cases of infant ALL, and t(9;22) with BCR-ABL fusion, also known as the Philadelphia chromosome (Margolin & Poplack, 2006). In recent years, minimal residual disease (MRD), which allows for detection of the smallest amount of leukemic cells during

treatment, has also been recognized as an important prognostic factor (Borowitz et al., 2003). MRD assays which are most useful are those based on polymerase chain reaction (PCR) amplification of antigen-receptor genes, and on flow cytometric detection of abnormal immunophenotypes. Higher levels of MRD have been associated with greater risk for relapse.

Specific treatment regimens for ALL vary, but all essentially emphasize several components: remission induction, CNS preventive therapy, consolidation, and maintenance or continuation therapy. CNS preventative therapy starts early and will be discussed in a different section in this chapter. All treatment starts with induction therapy over 4 to 6 weeks. The goal of induction is to achieve remission by eliminating more than 99% of the initial leukemic burden and restoring normal hematopoiesis. Approximate 98% of patients achieve remission by the end of induction (Pui & Evans, 2006). During induction, patients receive a three-drug therapy which includes vincristine, corticosteroids (prednisone or dexamethasone), and L-asparaginase in conjunction with intrathecal chemotherapy. Children with high risk features receive daunorubicin in addition to the three-drug combination. This four-drug induction chemotherapy, along with intensive consolidation and maintenance has improved survival for even high-risk patients (Gaynon et al., 1988). Current regimens favor the use of dexamethasone over the use of prednisone during induction and later phases of therapy. Various trials have demonstrated that dexamethasone is associated with better overall survival when compared to prednisone or prednisolone (Bostrom et al., 2003; Mitchell et al., 2005). Due to its longer half-life and better CNS penetration, dexamethasone appears to provide better CNS and systemic control than prednisone (Bostrom et al., 2003).

Consolidation is a course of intensified treatment that follows remission induction. High-dose methotrexate with mercaptopurine, high dose asparaginase and reinduction treatment are some commonly used regimens during consolidation (Pui & Evans, 2006). Intensive post-induction treatment with L-asparaginase has led to improved outcome (Margolin & Poplack, 2006). Several forms of L-asparaginase are available for use in the treatment of ALL, however, the dose and duration of treatment is more important than the form of L-asparaginase used (Pui & Evans, 2006). Maintenance or continuation therapy is the last phase of treatment. Maintenance entails a combination of monthly vincristine in combination with corticosteroids, oral Mercaptopurine (6-MP) and methotrexate (MTX) and intrathecal methotrexate every 3 months. The combination of 6-MP and MTX administered continuously in varying schedules is the principal component of maintenance therapy. MTX has been found to have optimal effect when it is administered weekly, whereas 6-MP is most efficacious when administered daily in the evening.

The adaptation of pediatric protocols to the treatment of adult ALL has led to improved outcomes, but there is still a significant gap in the success rate between the two age groups. Treatment of ALL in adults remains a major challenge with overall survival rates limited to 30–40% (Narayanan, 2011).

2.3 Therapy for CNS involvement
2.3.1 Systemic chemotherapy
Effective systemic chemotherapy has shown to improve control of CNS leukemia. Many current trials use high dose methotrexate (5 gram/m^2) as compared to the lower dose (0.5 to 1 gram/m^2) administered in the past. Other agents able to penetrate the blood brain barrier

and hence provide good CNS control include dexamethasone due to its longer half-life and low protein binding as previously mentioned. Results from the Children's Oncology Group (COG) have also shown that thioguanine at high doses provides effective systemic and CNS therapy (Stork et al., 2002).

2.3.2 Intrathecal chemotherapy

Intrathecal chemotherapy is an essential component of therapy for patients with clinically evident CNS disease (CNS 3). The three chemotherapeutic agents used most commonly through the intrathecal route are methotrexate, cytarabine and hydrocortisone. Methotrexate was the first to be administered through the intrathecal method. It is dosed by age, rather than weight. Some trials use triple intrathecals (methotrexate, cytarabine and hydrocortisone) or "IT triples". This arose from a study by the Pediatric Oncology Group which reported that the outcome for standard risk patients given IT triples was equivalent to those who received cranial radiation (Sullivan et al., 1982). Regardless of the chemotherapeutic agent selected for the intrathecal route, attention should be given to the dose to maximize therapeutic concentrations. Due to the anatomy of the brain and ventricles, only a small percentage of chemotherapy actually reaches the lateral ventricles. Several steps can optimize the therapeutic concentrations of chemotherapy in the ventricles. After a patient is infused with intrathecal chemotherapy, they should remain in the prone position for at least 30 minutes. This assists gravity in moving the chemotherapy to ventricles. Although intrathecal chemotherapy, particularly methotrexate, has improved outcome, it has produced a wide spectrum of acute and chronic neurotoxic sequelae, which will be discussed further in this chapter.

2.3.3 Cranial Irradiation

Aside from systemic and intrathecal chemotherapy, cranial irradiation is still recommended for patients who are CNS 3 at diagnosis. Cranial irradiation has replaced craniospinal irradiation. This shift is due to the fact that there is lack of evidence of the superior efficacy with craniospinal irradiation, along with the increased toxicity associated with spinal irradiation, including excessive myelosuppression, retardation of spinal growth and cardiac toxicity (Margolin & Poplack, 2006). In the COG trials (AALL0232, AALL0932, AALL0331) for patients who are CNS 3 at diagnosis, cranial radiation is given after successful induction of bone marrow remission. The dose of cranial irradiation is 18Gy (1800 cGy), which is administered in 10 daily fractions of 180 cGy per fraction to equal a total dose of 1800 cGy. The target volume consists of the entire brain and meninges. Although cranial irradiation is less toxic than craniospinal irradiation, its administration is not without short and long-term side effects. Many of these complications, which will be discussed in detail, include second malignancies, endocrinopathies, and neurocognitive deficits.

2.4 CNS relapse and risk factors

Decades ago, during the early years of treatment, survival was poor. However, in the 1960's, CNS relapse rose dramatically. Several investigators, including the Children's Cancer Group concluded that this rise was due to improved therapy leading to longer periods of remission and survival (Evans et al., 1970). Additionally, the CNS was the most common site of extramedullary relapse. With current treatment regimens, isolated CNS relapse has been reduced to <5% of pediatric cases of ALL (Laningham et al., 2007; Reiter et al., 1994). CNS

relapse accounts for approximately 30-40% initial relapses (Henze et al., 1991; Roy et al., 2005; Gaynon et al., 1998). CNS relapses can occur isolated, or in combination with bone marrow relapse.

The clinical impact and prognosis of CNS relapse is significant due to two factors. CNS leukemia is challenging to treat and CNS relapse eventually leads to bone marrow relapse. The Children's Oncology Group found that children with standard risk ALL who relapsed had better overall survival (OS) if they had isolated CNS relapse rather than combined relapse of CNS and bone marrow involvement (Malempati et al., 2007). Current protocols incorporate therapy to prevent CNS relapse. Intrathecal chemotherapy and intensification of systemic chemotherapy has largely replaced cranial radiation for prophylaxis of CNS relapse. These measures have successfully reduced the rate of CNS relapse. For the <5% of CNS relapses that occur, it is not completely clear why such relapses occur.

There are, however, several factors that can increase the risk of CNS relapse. Patients with hyperleukocytosis, T- cell ALL, Philadelphia chromosome, t(4,11) and the presence of leukemic cells in the CSF have been noted to have a greater risk of CNS relapse. Those with hyperleukocytosis in which the presenting white blood cell (WBC) is greater than 100 X 10^6/L and patients diagnosed with T-cell ALL were found to have the highest risk for CNS relapse. These subgroups of patients receive CNS-directed therapy which includes cranial radiation, along with intrathecal and systemic chemotherapy. High risk groups with cytogenetic abnormalities who are also at a greater risk for CNS relapse include ALL patients positive for Philadelphia chromosome (which produces a translation in chromosome 9 and 22) and those with t(4,11) (Pui, 2006). Approximately 50% of infants with ALL have the translocation in chromosome 4 and 11, also referred to as MLL gene rearrangement. Infant ALL with t(4,11) carries a poor prognosis. Iatrogenic introduction of peripheral blasts into the CSF also has the potential to increase CNS relapse. Thus, it is especially important to prevent a traumatic lumbar puncture at diagnosis, when circulating leukemic blasts are most abundant (Figure 2). Various studies have shown that a traumatic lumbar puncture is a risk factor for later CNS relapse and results in worse event-free survival due to iatrogenic introduction of blasts from the peripheral blood into the CSF (Burger et al., 2003; Gajjar et al., 2000; te Loo et al., 2006). Thus, lumbar punctures should be routinely performed by the most experienced clinician in the center. Other measures to minimize "bloody taps" include effective sedation/anesthesia to keep the patient still during the procedure and adequate correction of thrombocytopenia and coagulopathy prior to the diagnostic lumbar puncture.

3. Arguments for CNS prophylaxis in ALL

CNS prophylaxis therapy is based on the premises that the CNS is a sanctuary for leukemic cells, which are undetected at diagnosis and are protected by the blood brain barrier from systemically administered chemotherapy (Margolin & Poplack, 2006). The overall survival of pediatric ALL has significantly improved due to risk based therapy and CNS–directly therapy, with standard-risk ALL patients having a disease free survival rate of more than 90% in the United States and other developed nations (Schrappe et al., 2010). Though the CNS remains the most common site of extramedullary relapse, after intensive treatment less than 5% of patients with ALL will have CNS relapse (Laningham, 2007; Reiter, 1994).

CNS leukemia poses a challenge for treatment success and has a far worse prognosis. Thus, current treatment regimens continue to incorporate therapy directed at preventing CNS

relapse. CNS prophylaxis can be achieved by combinations of high dose systemic chemotherapy, intrathecal chemotherapy, and cranial or craniospinal radiation (Schrappe et al., 2010).

Effective CNS prophylactic regimens have resulted in a significant reduction in the incidence of CNS leukemia. In the 1970's, the first report was published which showed that the administration of intrathecal methotrexate with high dose cranial or cranial spinal radiation alone could improve the rate of CNS relapse from 50% to close to 10% (Aur et al., 1972). Investigators used either 24 Gy of cranial irradiation with serial doses of intrathecal methotrexate, or administered 24 Gy of cranial spinal irradiation alone. By the late 1970's , it became clear that although effective in improving CNS relapse, the intensive dose given in CNS-directed therapy caused significant acute and long term complications (Pizzo et al., 1979). This led to changes in therapy which eventually omitted craniospinal radiation altogether and reduced the prophylactic dose of cranial radiation from 24 Gy to 18 Gy as such changes were shown to be just as efficacious in preventing CNS relapse (Nesbit et al., 1981). In the mid -1990's, a trial conducted by BFM group showed that a reduced prophylactic dose of 12 Gy rather than 18 Gy provided effective CNS prophylaxis for high risk ALL (Schrappe et al., 2000). Despite the reduction in prophylactic cranial irradiation in contemporary regimens, the lower 12 Gy dose still results in substantial acute and subacute toxicities such as seizures, strokes, encephalopathies and late complications such as neurocognitive changes and second neoplasms. This has led to trials that have omitted cranial radiation for all patients. Trials by the St. Jude Children's Research Hospital and the Dutch Childhood Oncology Group report a good outcome for patients treated with high doses of intrathecal methotrexate post induction and increased frequency of triple intrathecal chemotherapy (methotrexate, cytarabine, hydrocortisone) with frequent vincristine/dexamethasone pulses (Pui et al., 2009 ; Verman, et al., 2009). It is important to mention that the prognosis of children with ALL living in less affluent nations-such as India (Arya et al., 2010) is different, even when the same radiation and chemotherapy protocols are used-with a CNS relapse rate of approximate 4%. Though much of the difference is probably attributable to the local conditions-such as poverty, illiteracy, inadequate facilities and therapy abandon, the remaining questions of different biological characteristics in different ethnic populations remains to be answered.

4. Cranial Irradiation for CNS prophylaxis

Although cranial radiation is an effective means of preventing CNS relapse for childhood ALL, its toxicity limits its use to a select group of patients. Only those who are considered high risk receive cranial irradiation for CNS prophylaxis. This subgroup of high risk patients include those who have T-cell ALL, have a high WBC at diagnosis (WBC ≥ 50,000/mL), were pre-treated with steroids within the week of diagnosis, and patients with certain cytogenetic abnormalities such as MLL rearrangements. Most current regimens do not administer cranial irradiation to infants or very young children, even if they are high risk (Pieters et al., 2007). Further, a review of 43 randomized trials reported that cranial irradiation is also not a necessary component of therapy for standard risk ALL (Clarke et al., 2003). For the high risk patients receiving CNS-directed therapy, cranial irradiation is initiated after patients have achieved bone marrow remission. It is generally administered during intensified consolidation. The prophylactic dose of cranial irradiation is 12 Gy (1200 cGy), given in 8 daily fractions of 150 cGy per fraction. The area that is targeted consists of

the entire brain and meninges, including frontal lobe as well as the posterior halves of the globes of eyes, optic disk and optic nerve.

5. Chemotherapy for CNS prophylaxis

Chemotherapy for CNS prophylaxis is delivered both systemically and intrathecally. All regimens for childhood ALL include either intrathecal methotrexate or triple IT (methotrexate with cytarabine and hydrocortisone). The dose of intrathecal methotrexate is based on age. For example, in the COG trials for ALL, the dose of intrathecal methotrexate is 8 mg, 10 mg, 12 mg, and 15 mg for children ages 1 to 1.99, 2 to 2.99, 3 to 8.99, and 9 years or greater, respectively. Similarly, the dose for intrathecal cytarabine is also age based: 30 mg, 50 mg, and 70 mg are administered for children ages 1 to 1.99, 2 to 2.99, 3 years or older, respectively. Intrathecal chemotherapy is initiated on the first day of induction therapy, in which three doses are given during the first four weeks of induction. Intrathecal chemotherapy is intensified during consolidation (approximately four to eight doses every two to three weeks). It is continued during maintenance, in which one dose of intrathecal chemotherapy is given every three months.

Systemic chemotherapy is also an important component of CNS prophylaxis. Systemically administered chemotherapy agents which provide effective CNS prophylaxis include dexamethasone, L-asparaginase, and high dose methotrexate with leucovorin rescue. All patients receive corticosteroid and L-asparaginase. Dexamethasone has become the corticosteroid of choice and is initiated during induction chemotherapy and continued during consolidation and maintenance. Depending on the regimen and the phase of treatment, the dose of dexamethasone varies. For example, during induction, the dose of dexamethasone can range as high as 10 mg/m2/day for high risk patients to a lower dose of 6mg/m2/day for standard risk patients. L-asparaginase is also initiated with induction chemotherapy and continues during intensified consolidation, although it is not included in most maintenance regimens. The dose is 2500 International units/m2/dose and it can be given intramuscularly or intravenously. High dose methotrexate is recommended for patients who are considered high risk. This includes patients with T-cell ALL, hyperleukocytosis with WBC ≥ 50,000/mL, aged 10 or older, received prior steroid therapy, or have testicular leukemia involvement at diagnosis. The dose of high dose methotrexate is 5 gm/m2/dose and is administered in conjunction with leucovorin rescue. It is administered during intensified consolidation in which four doses are given biweekly.

CNS Status	Lymphoblasts in CSF	WBC count (cells/mL)
CNS 1:	0	
CNS 2:	Present	<5
CNS 3:	Present	>/5 (or cranial nerve palsy)

Table 1. Definitions of CNS Disease at Diagnosis

Targeted therapies have not been used until recently in the treatment of ALL. However, most of the small-molecule tyrosine kinase inhibitors have excellent CNS entrance and a better safety profile, which makes them excellent candidates for CNS prophylaxis. The Children Oncology Group study of Imatinib treatment in children with Philadelphia chromosome-positive ALL reports outstanding early outcomes for patients treated with Imatinib and intensive chemotherapy (Schultz, 2009). Longer follow-up is needed to confirm

if this treatment also improves overall survival in these children who usually have poor outcomes.
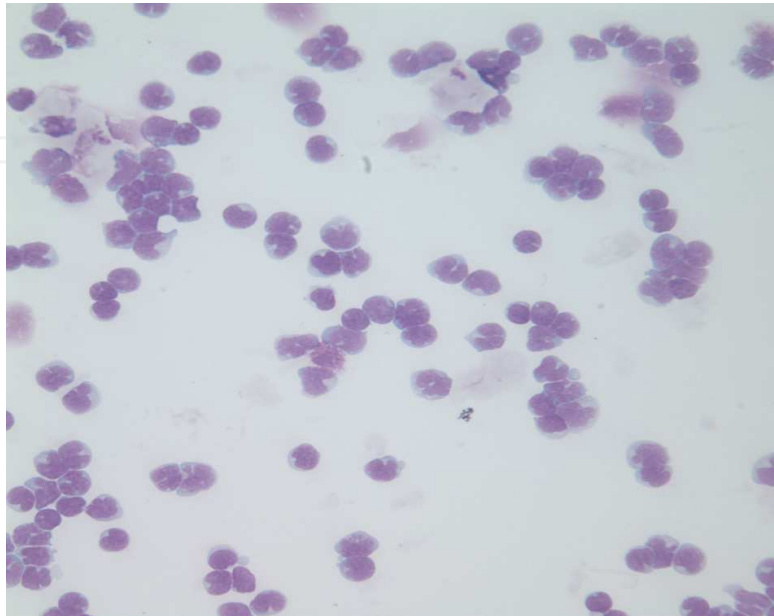

Fig. 1. CSF involvement in acute lymphoblastic leukemia. There are five or more white blood cells/mL with lymphoblasts. This appearance indicates CN S3 status (Wright-Giemsa stain; original magnification × 40, oil immersion) (Courtesy of Sachiv Sheth MD, CHOC Children's Hospital)
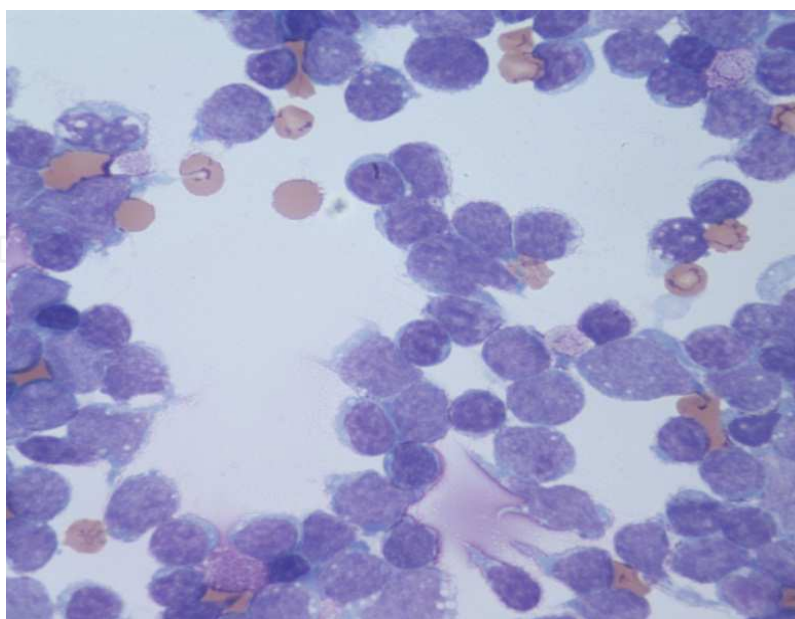

Fig. 2. CSF with lymphoblasts and RBC's due to a traumatic lumbar puncture (Wright-Giemsa stain; original magnification × 100, oil immersion) (Courtesy of Aaron Sasson MD, CHOC Children's Hospital)

6. Acute and sub-acute CNS complications after ALL treatment

6.1 Posterior Reversible Encephalopathy Syndrome (PRES)

PRES is defined by the clinical presentation of seizures, headaches, altered mental status and visual impairment. The imaging correlative is transient, bilateral lesions on T2/FLAIR sequences of MRI, predominantly affecting the occipito-parietal lobes. More than 40 cases of children with ALL who have developed PRES are described in the literature (Panis et al., 2010). Majority of the cases described happened during the induction phase (Gupta et al., 2008). Hypertension was one of the factors most commonly associated with PRES in children with ALL, however, in about 20% of the patients the blood pressure stayed normal. PRES treatment in children with ALL is mostly supportive, and includes anti-epileptic medications (AEDs) for seizures, and antihypertensive medications (beta-blockers, angiotensin converting enzyme inhibitors and/or diuretics). (Panis et al., 2010). Most patients recover without neurological complications, and do not require long-term AEDs, but rare cases of persistent epilepsy and even only one case of death have been reported (Hourani et al., 2008). As treatment delay is potentially lethal in ALL patients, the chemotherapy should be resumed after the resolution of neurological symptoms.

Since the majority of children with ALL receive multiple chemotherapeutic agents, it is hard to identify which of the drugs are responsible for PRES. However, multiple reports suggest an association between L-asparaginase (ASP) administrations and PRES (Kieslich et al., 2003). ASP is well-known to inhibit the hepatic production of proteins such as antithrombin and fibrinogen, and hence has the potential to induce transient thrombotic events which might contribute to the PRES etiology (Pound 2007).

6.2 Methotrexate toxicity: Leukoencephalopathy (Acute confusion, Seizures, Encephalopathy)

Methtrexate (MTX) is a folate antagonist widely used in the treatment of ALL . It inhibits methionine synthesis, an important metabolite necessary for CNS myelination (Linnebank et al., 2005), (Winick et al., 1992). CNS complications were described at different stages of treatment (such as acute, subacute or chronic). Acute MTX neurotoxicity ranges from 3–10% and varies with the dose and route of administration (Mahoney et al., 1998). The time from induction to the onset of acute neurotoxicity varies from 2 to 127 weeks and is more often seen 10–11 days after intrathecal MTX induction therapy.

Some of the neurological symptoms associated with MTX include headaches, nausea, emesis, lethargy, mental status changes, cognitive impairments, Kluver- Bucy syndrome, blurred vision, aphasia, transient or persistent hemiparesis, seizures, choreiform movements, arachnoiditis, encephalomyelitis, and death (Atra et al., 2004), (Antunes et al., 2002), (Asato et al., 1992), (Brock and Jennings, 2004), (Rubnitz et al., 1998). Leukoencephalopathy has been observed in less than 10% of patients after intravenous MTX administration, and up to 40% following intrathecal infusion (Atra et al., 2004), (Mahoney et al., 1998), (Rubnitz et al., 1998), (Lai et al., 2004).

The biological bases of MTX-induced neurotoxicity remain unclear. Various factors have been suggested for the effects of MTX such as: direct toxic effect on myelin, inhibition of glucose metabolism (Quinn et al., 2004), (Quinn et al., 1997), injury to oligodendrocytes, with disruption of myelin synthesis, disruption of mitochondrial energy metabolism resulting in oxidative stress and increased vulnerability of neurons to physiological glutamate concentrations (Rzeski et al., 2004), breakdown of the blood–brain barrier (Lai et

al., 2004) and inhibition of the enzyme dihydrofolate reductase, preventing the conversion of folic acid to tetrahydrofolic acid, thereby increasing the levels of homocysteine and excitotoxic neurotransmitters and inhibiting cell replication (Quinn et al., 2004), (Quinn et al., 1997).

Diagnostic Tests	Reported Results
CSF Analysis	Normal or sterile pleocytosis
MRI	White matter abnormalities (usually transient) Microcalcifications
EEG	Focal or diffuse slowing Epileptiform activities
Magnetic Resonance Spectroscopy	Metabolite changes

Table 2. Diagnostic Tests in Suspected Cases of Methotrexate Neurotoxicity
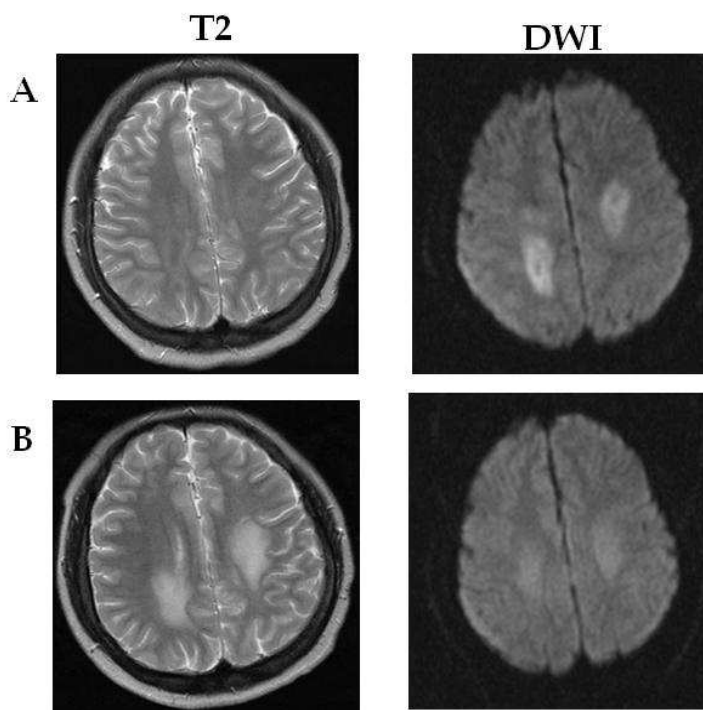

Fig. 3. Brain MRI in a patient with acute MTX toxicity. A. At time of initial diagnosis, hyperdense lesions are noted bilaterally on DWI in the centrum semiovale. B. Two months later. The patient's symptoms (seizures, paralysis) resolved.

MTX neurotoxicity is in the differential diagnosis for any ALL patient with acute neurologic findings and previously treated with the folate antagonist (see Table 2). In this population, CSF analysis is usually unremarkable (Table 3). Electroencephalographic findings are

usually non-specific. Acutely, MRI-DW studies show white matter changes that are probably due to demyelination (Rollins et al., 2004), (Ebner et al., 1989), (Sandoval et al., 2003). Magnetic resonance spectroscopy may demonstrate metabolite changes in the absence of structural white matter abnormalities (Davidson et al., 2000).

The treatment of acute MTX toxicity is still under research (Bota and Dafer, 2009). MTX neurotoxicity was reported to be reversible with administration of dexamethasone and leucovorin (Shuper et al., 2000), (Cohen, 2004). Leucovorin antagonizes the effects of MTX on purine metabolism through maintenance of DNA/RNA synthesis, despite the blockade of dihydrofolatereductase. Significant improvement of neurological symptoms has also been achieved with combined administration of aminophylline - an adenosine antagonist - and high-dose folinic acid (Jaksic et al., 2004). Whether glutamate antagonists could prevent neurotoxicity of MTX when given with cancer chemotherapy remains to be determined (Murphy et al., 1999).

7. Long-term CNS complications after ALL treatment

7.1 Neurocognitive complications

As the number of long-term ALL survivors is progressively increasing, more and more attention is drawn to their long-term cognitive effects and to the quality of life. As majority of the patients are diagnoses during early childhood, the neurodevelopmental sequelae are mostly the effects of CNS-directed therapies on the developing brain (Temming and Jenney, 2010).

Cranial radiation has been long associated with deleterious effects on cognitive function-especially on verbal intelligence quotient and achievement tests of reading, spelling, and arithmetic, directly proportional with the radiation dose (Moore et al., 1991). Though the results of neurocognitive outcomes are heterogenous, a large meta-analysis has shown that, when measured across 30 comparisons in 20 different studies, an average intellectual quotient (IQ) decrement of about two-thirds of a standard deviation, or about 10 points, follows CNS prophylaxis that includes cranial irradiation (Cousens, 2006). The results of the meta-analysis also showed that children irradiated at a younger age (younger than four) are more seriously affected than older children. Girls also tend to be more affected by the CNS radiation treatment, with a higher prevalence of learning disabilities and lower IQs (Waber et al., 1990). Usually, cranial radiation is administered in combination with intrathecal MTX, which has potential additional neurotoxicities, especially in girls-with a demonstrated decreased intelligence quotient (IQ estimate, 9.3 points) when high-dose MTX (4 g/m²) during induction was followed by cranial radiation (Waber 1995).

Chemotherapeutic prophylaxis has less deleterious effects in absence of radiation (Krappmann et al., 2007), with a slight but significant decline of the IQ score only in younger children and girls.

Another potential risk factor is allogeneic hematopoietic stem cell transplantation-with significant deficits immediately after transplantation (Syrjala 2011). Although neurocognitive function improved from 1 to 5 years after transplantation, deficits remained for more than 40% of survivors, especially in motor dexterity and verbal learning and retention.

Neuroimaging structural changes in the executive areas of the brains of ALL survivors are also well described-and between 16% and 52% of those who have received treatment for ALL experience at least one brain abnormality (Porto 2004). Additionally, ALL survivors

displayed significant abnormalities in functional imaging, with greater activation in areas underlying working memory (dorsolateral and ventrolateral prefrontal cortex) and error monitoring (dorsal and ventral anterior cingulate cortex), which correlate with poor performance on working memory tasks (Fuller et al., 2009).

7.2 Behavioral disturbances and Attention deficit syndromes

As mentioned in the previous paragraphs, neuro-cognitive impairments are widely present in the ALL survivors. In addition, many survivors also have multiple behavioral symptoms suggestive of attention deficit/hyperactivity disorder (ADHD) (Krull et al., 2011). These abnormalities are assessed by behavioral ratings- especially from the family and classroom teachers. A recent survey of the parents of adolescent cancer survivors (almost 50% of them had leukemia) and their healthy siblings identified that the ALL survivors had significantly higher rates of parent- reported attention deficits, as well as of depression/anxiety and antisocial domains (Schultz, JCO 2007). More than one half of survivors (54%) received intrathecal methotrexate, cranial radiation, or both and treatments with cranial radiation and/or intrathecal methotrexate were specific risk factors for depression/anxiety, attention deficit, antisocial behaviors, and diminished social competence.

Attention problems are commonly reported in these patients (up to 25.5% of the survivors), but the rate of patients meeting the full criteria for ADHD is only of 10.5%- just slightly higher than the reported rate in the general population (Krull et al., 2011). Also, similar rates of ADHD were seen in boys and girls, and especially in the patients that have received cranial radiation therapy. Most of the patients had more inattention as compared with the general population (where hyperactive and impulsive behaviors are more common) which suggests that the cancer survivors might have a different phenotypic ADHD. One hypothesis is that attention difficulties in ALL survivors may be related to genetic variations such as polymorphisms of the folate pathway rather than dopamine transport or reuptake, as suspected in developmental ADHD (Krull et al., 2008).

The treatment of attention problems encountered by survivors of ALL is open for debate. A prospective, placebo-controlled, crossover trial of medications (methylphenidate) was successful in a significant number of the patients (45%) (Conklin et al., 2010), however the percentage of responders is much lower than the one reported in general ADHD population (75%) (Greenhill et al., 2001). Alternatively, a pilot study of computerized cognitive treatment suggests some benefit, but larger studies are needed to confirm clinical value (Hardy et al., 2011).

7.3 Cerebrovascular disease

As previously mentioned, radiation therapy had a major effect in improving the survival of ALL patients. However, the normal tissue damage associated with CNS radiation can be profound, and is not limited to the neural cells. The vascular response to radiation includes arteries of all calibers (small, medium and large), and can occur either acutely or as late as many years after the initial treatment (Morris et al., 2009). As such, the ALL survivors have a high risk of developing intracranial steno-occlusive disease (moyamoya disease) as well as vascular malformations (telengiectasias, cavernomas and rarely aneurysms).

Moyamoya disease is commonly seen in Asian populations and children. The Tokyo Children's Cancer Study Group reported the largest series of ALL patients evaluated for moyamoya, and found a cumulative incidence of moyamoya disease of 0.46% at 8 years-20

fold higher that the incidence in general Japanese population. None of the six patients with moyamoya had CNS involvement at the initial ALL diagnosis, and all of them received prophylactic cranial irradiation (Kikuchi et al., 2007). Majority of the children (4/6) improved after surgical revascularization, while one child died of extensive strokes before the procedure could be attempted.

Telengiectasias are the most commonly described vascular malformations in ALL survivors (Morris et al., 2009). The rate of telengiectasia was reported for the leukemia survivors to be 16%, in spite of the fact that almost all patients received only 18 Grays. The majority of the lesions were small, and the patients tended to remain asymptomatic during the duration of the study (five years) (Koike, 2003).

A study of long-term survivors of childhood tumors reported that the rate of strokes for leukemia survivors was 57.9 per 100,000 person-years (95% CI, 41.2 to 78.7), and the relative risk rate of stroke for leukemia survivors compared with the sibling comparison group was 6.4 (95% CI, 3.0 to 13.8; $P < .0001$) (Bowers 2006). Mean cranial radiation therapy dose of > or = 30 Gy was associated with an increased risk of stokes in a dose-dependent fashion. This increased incidence of strokes might be caused not only by the radiation-induced vascular damage but also by the high rate of metabolic abnormalities such as obesity, insulin resistance and low high-density lipoprotein levels seen in adult survivors of childhood leukemia (Talvensaari et al., 1996). The highest at-risk population is represented by the patients that have received hematopoietic stem cell transplantation with total body irradiation, and who had a very high rate of hypertriglyceridemia, low level of high-density lipoprotein cholesterol, and elevated fasting glucose (Oudin, 2011).

7.4 Secondary CNS malignancies: Meningiomas and gliomas

Cranial tumors following high-dose CNS radiation for childhood ALL have been reported initially (Tiberin et al, 1984a; Tiberin et al. 1984b). The cumulative rate of a secondary brain tumor is about 18-20% (Pui, Goshen), with the most common tumors being overwhelmingly meningioma, and less commonly gliomas.

A retrospective study of the ALL patients treated with radiation between 1974 -1989 at the Schneider Children's Medical Center of Israel determined that 18 out of 88 survivors developed meningiomas (Goshen et al., 2007). The initial diagnosis of ALL was made 10-29 years earlier, with a median interval of 21 years, and the rate of meningiomas considerably increased after 15 years from therapy. There was no female predominance- as is usually seen in the general population, and all of the meningiomas discovered were WHO grade I. One additional case of low-grade glioma was also identified.

Though the gliomas are rarer, they are a serious cause of concern in survivors of childhood cancer. The results from the British Childhood Cancer indicate that the 5 year relative survival for these patients is very poor-only 19.5%. The interval between the childhood cancer and glioma development was 15.5 years for the low-grade gliomas, 18.7 years for the anaplastic gliomas and 21 years for glioblastoma multiforme (Taylor et al., 2009). The long-term results of the Tokyo Children's Cancer Study group trials for ALL identified secondary brain tumors (gliomas) in 12 out of 1846 patients (Tsuchida et al., 2010). All the patients received cranial radiotherapy as part of their treatment, and the secondary tumors developed after 8-22 years after the initial treatment. There was an equal sex distribution. The cumulative incidence was 1.9% at 15 years, and 2.8% at 20 years. These numbers are very similar with the St Jude report of a cumulative incidence of brain tumors except

meningioma of 3% at 30 years (Hijiya et al., 2007). Majority of radiation-induced gliomas are of astrocytic origin (Walter et al., 1998), however a few low grade and anaplastic oligodendrogliomas are also reported (Alexiou et al., 2010). These patients received standard treatment with focal brain radiation (50 Gray), followed by PCV chemotherapy. In patients with relapsed ALL, the rate of secondary CNS malignancies (glial in origin) was very low-2 out of 1376 patients, in spite of intensive second-line treatment. In general, the rate of secondary malignancy was found to be significantly associated with stem cell transplantation, and high cumulative doses of cranial irradiation, etoposide and cyclophosphamide-however the numbers are too small to conclude for CNS malignancies (Borgmann et al., 2008).

The use of intrathecal and systemic chemotherapy instead of cranial radiation has led to a reduced rate of secondary CNS tumors. The just-published results of the EORTC 58881 trial which did not include cranial radiotherapy showed a very low rate of secondary malignancies, with only one patient out of 2,261 enrolled being diagnosed with glioblastoma multiforme (Renard et al., 2011).

Our own experience at the UC Irvine Chao Cancer Center and the Children Hospital of Orange County is that often the secondary meningiomas in ALL survivors are atypical or anaplastic (see figure 4). The treatment of these patients is very difficult due to the fact that they have already received brain radiation, which is the standard of care and the only proven treatment for malignant meningiomas. Early diagnosis of secondary brain tumors allows for surgical approaches before the tumors become symptomatic. As the ALL patients live longer, a yearly neurological exam and periodic brain MRI's in search for intracranial lesions should be considered for those who received cranial or craniospinal radiation.
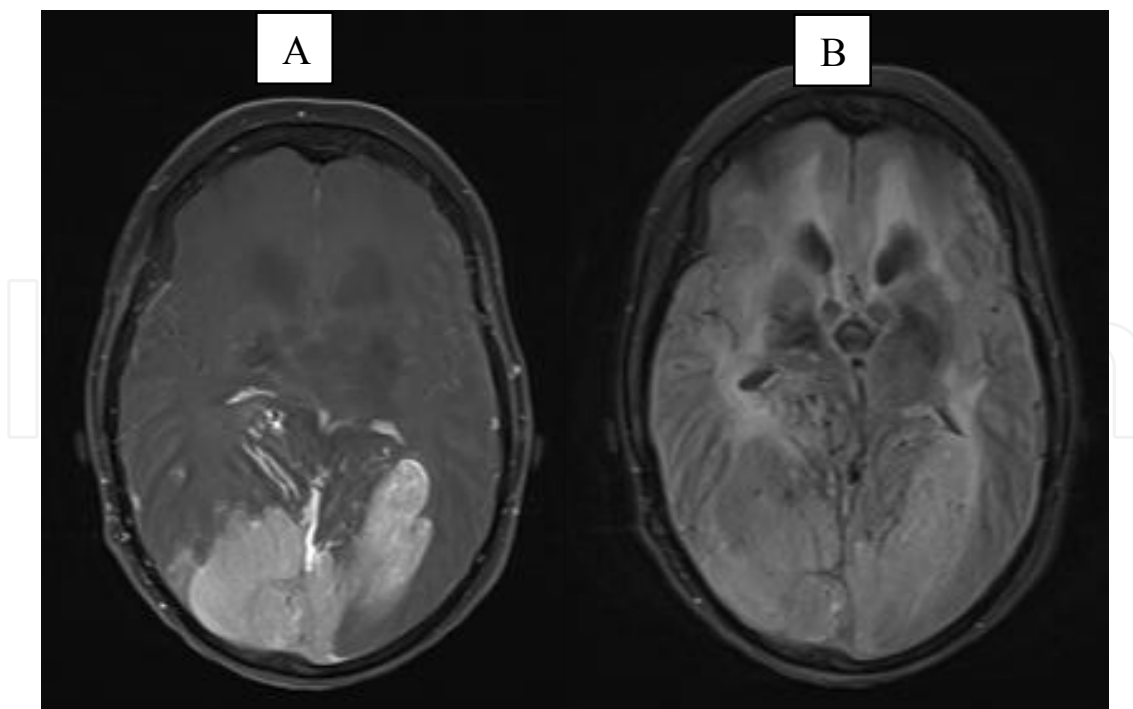

Fig. 4. Brain MRI in a patient with multiple malignant meningiomas and brain atrophy. The patient has received cranial radiation for ALL 18 years prior to the initial meningioma diagnosis.

8. Further directions: Neuroprotective and restorative treatments

The long-term implications of CNS-directed treatment in the life of ALL patients are very profound. A long-term study (twenty-five year follow-up) reported more adverse general and mental health, functional impairment, and activity limitations in ALL survivors compared with siblings. Rates of marriage, college graduation, employment, and health insurance were also all lower compared with sibling controls (Mody R, 2008). Hence, modalities to either limit the CNS toxicities or to restore the lost function have the potential to significantly improve the long-term outcome.

Radiation is well-known to affect different brain structures, including the neural stem cells as well as the glial and vascular (Sundgren and Cao, 2009), (Acharya et al., 2010). In addition, majority of the chemotherapeutics used for ALL treatments have numerous effects on the brain, increasing the oxidative stress, reducing neurogenesis, affecting the blood flow and generating white matter damage (Seigers and Fardell, 2011). Previous research has shown that some chemotherapy drugs including cytosine arabinoside as well as radiation (Monje et al., 2002) are toxic at therapeutic doses for the neural stem/progenitor cells (Seigers et al., 2008).

There are very few studies looking at the cognitive consequences of chemotherapeutic agents in animal models (Seigers et al., 2008), (Foley et al., 2008), (Winocur et al., 2006), (Reiriz et al., 2006), (Lee et al., 2006), (Macleod et al., 2007). Single dose administration of methotrexate impairs spatial memory, prolonging latency to finding the platform in the Morris water maze test, and impairing the novel object recognition (Seigers et al., 2008), hence suggesting hippocampal damage. Administration of multiple doses of methotrexate causes deficits in spatial and non-spatial memory, showing the importance of studying the effects of chronic chemotherapy (Winocur et al., 2006).

Hippocampal dedritic spine damage is found after single-dose administration of cyclophosphamide in hippocampal slices, and causes transient impairment of long-term potentiation (Lee et al., 2006). Clinically, reduced hippocampal volume and loss of neurogenesis have been found in chemotherapy treated colon cancer patients (Schneiderman, 2004) and brain tumor patients[37], respectively, though no clear changes were found in ALL survivors (Hill et al., 2004). However, the attention and memory deficits present in ALL patients might suggest a functional deficit even if no structural changes are clearly defined.

Limiting the toxicity of presently-used regimens is a subject of intense research. Elimination of radiation has played a significant role in limiting toxicity. Developing active chemotherapy agents that can limit CNS toxicity while still offering low-rates of CNS relapse will constitute the next step. Our recently-published work (Bota 2009) suggests that pathway targeted agents (such as tyrosine kinase inhibitors or proteasome inhibitors) might have *in vitro* a more favorable, neural stem-cell sparing profile than the classic DNA-targeted agents.

Reversal of neuropsychological late effects has been attempted through cognitive remediation, and ecological manipulations of the classroom environment (Mulhern and Butler, 2004). These methods are based on the treatment of traumatic brain injuries, and have moderate success in the treatment of ALL survivors (Butler et al., 2008). Specific modalities using computer-based cognitive training, which could be used at home by the patients in more remote communities, has the potential to improve working memory and

decrease parent-rated attention problems and to bring further promise for ALL patients (Hardy et al., 2011).

Finally, medications that can either increase patient attention and concentration (based on the promising methylphenidate studies) or reverse the CAN damage (such as medication which can stimulate neurogenesis) should be further researched and better understood.

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10. References

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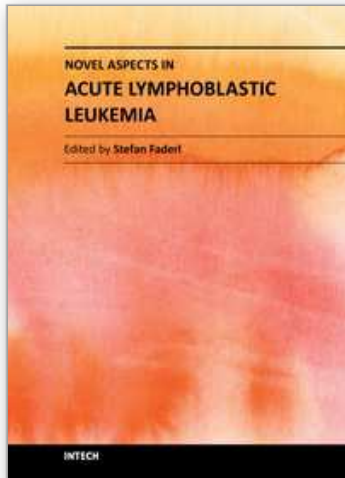
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Acute lymphoblastic leukemia (ALL) has turned from a universally fatal to a highly curable disease in little more than four decades. Even though differences in outcome continue to exist between children and adults, intense efforts are under way to 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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