The Libyan International Medical University

Faculty of Basic Medical Science

The spectrum of CNS relapse during treatment of acute lymphoblastic leukemia

Mohammed eltajoure

2158

Supervised by: Essam eldana

Assisted by :Lujain shakmak

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Abstract :

During therapy for acute lymphoblastic leukemia (ALL), children with central nervous system (CNS) toxicity are at risk for treatment changes, long-term squeal, and evenhigher mortality a better understanding of CNS symptoms and their complications enhances the potential for their prevention and treatment ,despite all the advances in the treatment of childhood acute lymphoblastic leukemia, central nervous system relapse remains an important obstacle to curing these patients.

The survival of children with acute lymphoblastic leukemia (ALL) has greatly improved in the last 40 years with rates of up to 80% among the main referral centers, Relapse of ALL is the main cause of treatment failure,It may occur at a single extra medullary site or concomitantly with marrow relapse .

This study will analyze the incidence of central nervous system relapse and the risk factors for its occurrence in children with acute lymphoblastic leukemia .

Introduction :

Acute lymphoblastic leukemia (ALL) is the most common form of childhood cancer, it is a systemic disease that arise from several cooperative genetic mutations in a single B or T lymphoid progenitor, leading to altered blast cell proliferation , survival, and maturation, and eventually to the lethal accumulation of leukemic cells with the tendency for post-therapeutic recurrence in the central nervous system and causes Relapse of (ALL) which is the main cause of treatment failure It may occur at a single extra medullary site or concomitantly with marrow relapse.(M. & W., 2018)

The treatment directed at the (CNS) was one of the major advances for improving survival of (ALL) during the last decades , It consists in the administration of intrathecal chemotherapy, high dose systemic chemotherapy and cranial radiotherapy.(F. & H., 1980)

The majority of treatment protocols restricts radiotherapy to a small group of patients, based on already established risk factorsRecent studies aimed to decrease and eventually exclude irradiation from first-line (ALL) treatment By replacement irradiation with additional intensive CNS-directed therapy each the dose and route of administration of the drug might influence neurotoxicity.(Pui et al., 2009)

Methods and materials :

Patient files from 649 children treated with Nordic Society of Pediatric Hematology and Oncology ALL92 and ALL2000 protocols in Finland were reviewed retrospectively for any acute (CNS) symptom , Detailed data on symptoms examinations and treatment of the underlying (CNS) complications were collected from the medical recordsDisease-related and outcome data were retrieved from the Nordic leukemia registry(Banerjee et al., 2020).

Results :

In total, 86 children out of 643 (13%) developed acute CNS symptoms during ALL treatment. Seizures were the most common symptom (67%), followed by visual disturbances (23%) and headache (12%), PRES was the most common complication behind the symptoms (4.5%, n=29). Cerebrovascular events occurred in 10 patients (1.6%,), while SLS was rare.(Banerjee et al., 2020)

Figure 1 : The cumulative incidence of relapses in patients with defined central nervous system (CNS) complications and no defined CNS complications (systemic or unclear conditions with CNS symptoms or no CNS symptoms.(Banerjee et al., 2020)

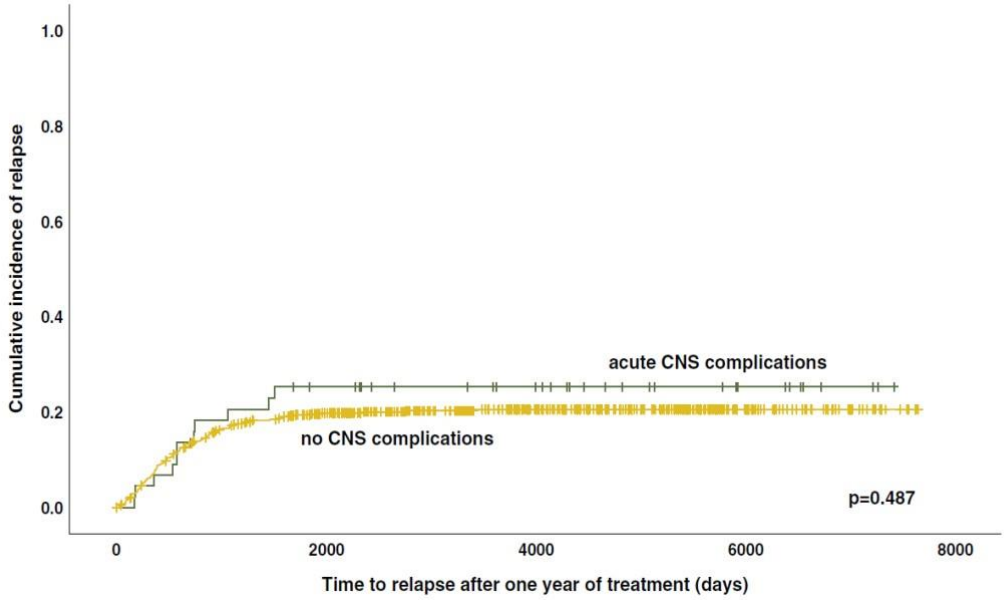

Table 1 : The spectrum and frequency of central nervous system (CNS) symptoms in the study population and in different underlying etiologies .

One (CNS) complication may have caused several different (CNS) symptoms.(Banerjee et al., 2020)

Patients with CNS symptoms (n = 86)	**Seizure (generalized/ focal epileptic) n = 63 (73%)**	**Visual disturbances n = 24 (28%)**	**Flabbiness, altered level of consciousness n = 23 (27%)**	**Persistent headache n=10 (21%)**	**Absence n = 8 (9%)**	**Hallucinations/ confusion n = 7 (8%)**
Posterior reversible encephalopathy syndrome (n = 29)	29 (100%)	13 (45%)	4 (7%)	5 (17%)	2 (7%)	4 (14%)
Hypertensive encephalopathy (n = 6)	6 (100%)	2 (33%)	3 (50%)	-	1 (17%)	-
Cerebrovascular (n = 10)	4 (40%)	3 (30%)	3 (30%)	5(50%)	1(10%)	2 (20%)
Methotrexate related stroke-like syndrome (n = 1)	-	-	-	-	-	-
Encephalitis (n = 4)	2 (50%)	1 (25%)	3 (75%)	-	-	-
Systemic or unclear conditions with CNS symptoms (n = 36)	22 (61%)	5 (14%)	10 (28%)	-	4 (11%	1 (3%)

Discussion :

In our nationwide study, 13% of the patients treated for (ALL) suffered from acute CNS symptoms during their treatment, creating a significant clinical challenge. PRES and cerebrovascular events were the most common etiologies causing (CNS) symptoms (n = 39, 6%). However, systemic conditions with (CNS) symptoms, especially systemic infections, were important for differential diagnosis. SLS was remarkably rare. The majority of events occurred during the first 2 months of therapy. In our series, (CNS) toxicity was not associated with poorer leukemia-free survival. The incidence of acute neurotoxicity has varied between 3 and 18%, depending on the capturing system and inclusion criteria.(Banerjee et al., 2020)

The study population in previous studies has been heterogeneousmaking comparisons difficult ,Some studies have included seizures that had occurred in relapsed patients, before diagnosis of (ALL) or after cessation of therapy, further six larger studies solely reported incidences of acute (CNS) toxicities, whereas many studies included even peripheral neuropathy, long-term neurocognitive defects or late-onset encephalopathy, In line with our study, acute (CNS) symptoms have often been reported during induction treatment (range 29-57%).In our study, over half of all (CNS) symptoms occurred during early treatment and were likely related to intensive chemotherapy, immunosuppression or direct effects of leukemia. In our study, defined (CNS) complications were more common in patients with (CNS) involvement at diagnosis and T-cell immunophenotype, and in patients who received high-risk treatment. Only (CNS) leukemia, however, was an independent risk factor in the multivariate analysis (Vora et al) showed in the large UKALL2003 study that patients treated with higherrisk protocols had an increased risk of toxicities in general, including seizures and encephalopathy.(Banerjee et al., 2020)

Age and female gender were not associated with an increased risk of (CNS) toxicities in our study. but they have been linked to (CNS) toxicities by others .
As the treatment approaches differ, it is becoming increasingly important to distinguish between different etiological entities, Patients with SLS may benefit from N-methylD-aspartate-receptor antagonists, while patients with PRES benefit from the management of blood pressure and patients with SVT require anticoagulation.(Banerjee et al., 2020)

PRES has been recognized as a separate entity only for two decades, as the symptoms overlap with other toxicities,22 Of note, a recent study by (Milan et al) did not report any cases of PRES, although the majority of neurological toxicities occurred during induction, with seizures being the most common presenting symptom. The most common (CNS) toxicity in their series was MTX leukoencephalopathy, and the diagnosis was based on neurological symptoms appearing within 2 weeks of MTX administration, Therefore, we assume their definition of MTX leukoencephalopathy may also have included PRES in our study.(Banerjee et al., 2020)

PRES was the most common, comprising one third of all (CNS) complications Participants of this study showed the highest incidence of PRES compared to those in previous studies, although it has been the most common complication in relation to other (CNS) toxicities in some previous studies ,The intensive use of VCR may partially explain the higher incidence of PRES in our study, In older studies seizures with no apparent cause were the most common (CNS) symptoms Therefore, the differences in the incidences of PRES can be explained either by the use of different protocols or at least earlier, by the limited availability of MRI and the poor recognitionand diagnosis of PRES.(Banerjee et al., 2020)

PRES and hypertensive encephalopathy areoverlapping syndromes, so in many cases patients with PRES fulfill criteria of hypertensive encephalopathy as well. In the current study,patients with PRES and hypertension met the criteria for hypertensive encephalopathy, whereas patients with hypertensive encephalopathy did not fulfill the criteria for PRES, as they had either undergone no imaging or only (CT) without typical radiological findings, Whether the patients with hypertensive encephalopathy in fact had PRES remains unclear, since its diagnosis requires typical imaging finding (bilateral vasogenic edema), which (CT) can easily fail to demonstrate .
In our study, the incidence of SVT was 0.8%, which is at the lowend of the incidences reported in the literature (Parasoleet al) did not observe any SVT cases, Headaches were the main symptom in our patients .

A variety of other neurological symptoms were also observed, In all five patients, SVT was associated with asparagines treatment, a well-recognized risk factor for thrombogenicevents. Previous reports on age as a risk factor for SVT havebeen

contradictory , In our study, older age was not associated with SVT, as all five patients were under 10 years at diagnosis, Despite intensive MTX treatment in our protocols, MTX-inducedSLS was a remarkably rare event. In other studies, the incidence hasbeen higher, varying between 0.8 and 3.8% ,SLS is usually easy to recognize, both symptomatically and in terms of timing.(Pui et al., 2009)

Therefore, we believe (CNS) symptoms related to SLS would have either been diagnosed or at least mentioned in patient files ,but we cannot exclude underreporting concerning mild or non-typical SLS ,In addition, the oldest patients were diagnosed in the early 1990s, at the time of the earliest reports of SLS,(CNS) symptoms related to systemic conditions, especially to infections,were relatively common in children, accounting for almost half of all causes of (CNS) symptoms ,(Ochs et al) reported infections orencephalitis as the most common diagnosis for seizures of a known etiology however, the majority of seizures were of an unknown etiology.

Even if patients with (CNS) toxicity did not have a worse overall survival after the first year of treatment, it caused both acute and long-term morbidity ,One fifth of our patients developed epilepsy, and a majority of them had previously had PRES Epilepsy is therefore likely associated especially with PRES, as reported both in our previous study and in other studies, where the incidence of epilepsy varied from 12 to 30%. This large, population-based study comprises all hematology units in Finland, The coverage from patient files is almost complete (99%). Adverse events are better recognizednowadays, We believe that significant neurologic symptoms were mentioned in the patient files, which makes our results reliable, We had strict criteria for complications, minimizing the risk of overestimating the incidences.

Conclusions:

In conclusion,(CNS) symptoms are frequent and occur most often during the first 2 months of treatment. Besides defined (CNS) complications PRES, hypertensive encephalopathy, cerebrovascular events, encephalitis and SLS Systemic conditions, such as infections, are frequent causes of (CNS) symptoms, Although defined(CNS) complications are mostly reversible, some are life threatening, and long-term adverse effects do exist , Better recognition, treatment and prevention of (CNS) complications

are some of the most important challenges in the improvement of leukemia treatment.(Banerjee et al., 2019) .

This report suggest that a leukocyte count (> 50 x 10/L) at diagnosis seems to be a significant prognostic factor for a higher incidence of central nervous system relapse in childhood acute lymphoblastic leukemia .

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