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Original Research Article

Evaluating the Role of Intrathecal Chemotherapy in CNS Prophylaxis for Pediatric Leukemias: A Retrospective Study

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Abstract: *The central nervous system (CNS) is a sanctuary site for leukemic cells in pediatric acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), necessitating targeted prophylaxis.* ***Objective:*** *To evaluate the effect of IT chemotherapy intensity on CNS relapse-free survival (CNS-RFS) in pediatric leukemia patients.* ***Methods:*** *This retrospective observational study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Center from 2023 to 2024. A total of 150 pediatric patients (118 ALL, 32 AML) were included in the study. Patients were categorized as receiving full-intensity (≥90% of planned IT doses) or reduced-intensity (<90%) CNS prophylaxis.* ***Results:*** *Of the cohort, 108 patients (72.0%) received full-intensity IT chemotherapy and 42 (28.0%) received reduced-intensity. Over a median follow-up of 48 months, CNS relapse occurred in 4 patients (3.7%) in the full-intensity group versus 10 patients (23.8%) in the reduced-intensity group ($p < 0.001$). Five-year CNS-RFS was significantly higher with full-intensity prophylaxis (96.0% vs. 71.4%, $p < 0.001$). Multivariable analysis showed reduced-intensity IT was independently associated with increased CNS relapse risk (HR 4.85; 95% CI: 1.78–13.21; $p = 0.002$). Neurotoxicity occurred in 7.3% of patients, mostly reversible, and procedural complications occurred in 5.3%, with no permanent deficits.* ***Conclusion:*** *Full-intensity IT chemotherapy is strongly associated with lower CNS relapse rates and improved CNS-RFS in pediatric leukemia, particularly in high-risk subgroups. Minimizing treatment interruptions and addressing logistical barriers are essential to maintain optimal CNS prophylaxis, especially in the era of reduced cranial irradiation.*

Keywords: Pediatric leukemia, CNS prophylaxis, intrathecal chemotherapy, CNS relapse, acute lymphoblastic leukemia, AML

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Introduction

Pediatric leukemias, most notably acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), constitute the most prevalent childhood cancers, representing approximately 30–35% of all malignancies in patients under the age of 15 (1). The overwhelming majority of pediatric leukemia incidences are referred to as ALL at around 75 percent, whereas the bulk of the non-ALL cases belong to AML (2). Optimization of systemic chemotherapy regimens, risk stratification, and supportive care have dramatically changed outcomes of these diseases, and now in high-income countries, more than 85% of patients with standard-risk ALL survive. Nevertheless, although these treatments have offered the therapeutic advantage, the central nervous system (CNS) has remained the most important place of relapse of the disease. In history, the CNS was one of the main causes of treatment failure and death (3). CNS forms a pharmacologic sanctuary to leukemic cells owing to the constraining nature of the blood-brain barrier (BBB)/ blood-CSF barrier. Such physiological obstacles greatly impede dispersal of the majority of the systemic chemotherapeutic agents, allowing residual leukemic cells to continue residing within the meninges, CSF, or in the brain parenchyma in cases where systemic disease also seems in remission (4). Without CNS-directed therapy, relapse levels in the CNS during treatment or immediately after unsuccessful treatment may be as high as 3050%, and once CNS relapse intervenes, the chances of remission in sustaining remission are significantly minimized (5). Intrathecal (IT) chemotherapy cuts to the chase by overcoming this sanctuary issue by avoiding the BBB to instead introduce therapeutic agents directly into the CSF. This permits a large amount of local drug concentration and very low systemic exposure. Some of the commonly used IT agents are methotrexate, cytarabine, and hydrocortisone alone, or in combinations such as triple intrathecal therapy (TIT) (6). Methotrexate acts as a cytotoxic drug by inhibiting dihydrofolate reductase, thereby impairing DNA synthesis in cells. Cytarabine, on the other hand, interferes with the DNA replication process by binding to DNA strands and DNA polymerase (7). Hydrocortisone, as an anti-leukemic steroid and as a way to alleviate meningeal inflammations due to the chemotherapeutic agents, has been added. In the past, the use of cranial irradiation played a significant role in CNS prophylaxis in pediatric leukemia, besides the systemic and intrathecal therapy (8). Although it has proven to be effective in lowering CNS relapse rates, cranial irradiation has had major long-term toxicities, which include neurocognitive deficits, growth retardation, endocrinopathies, and secondary malignancies. In the last 30 years, the trend in cooperative group trials has been to abdicate or limit cranial irradiation in favor of more intense IT and systemic CNS-directed chemotherapy in all patients, but especially those at low-standard and intermediate risk (9). Clinical evidence has also supported this new change as it has shown that when properly administered, chemotherapy-based CNS prophylaxis achieves the same levels of relapse as the regimes that include cranial radiation, but with significantly fewer late effects (10). IT chemotherapy is commonly supplied during ALL induction, consolidation, and maintenance, and its repetition and frequency rely on patient CNS status at the beginning of treatment, general risk assessment, and the accompanying treatment strategy (11). A more aggressive CNS-directed treatment may be especially indicated in high-risk characteristics of CNS involvement at the initial diagnosis (CNS3 status), T-cell phenotype, hyperleukocytosis, or poor cytogenetics (12). CNS prophylaxis within AML is not as standardised but would usually be administered to all patients in induction with the additional benefits in those who present with CNS involvement or other high-risk features (13). Thus, the study aims to evaluate the effect of IT chemotherapy intensity on CNS relapse-free survival (CNS-RFS) in pediatric leukemia patients.

Methodology

This retrospective observational study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Center from 2023 to 2024. A total of 150 children (≤18 years) with newly diagnosed acute leukemia were included. Eligible diagnoses comprised acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), confirmed by morphology, immunophenotyping, and cytogenetics/fluorescence in situ hybridization per institutional standards.

Children aged 0–18 years with de novo ALL or AML; initiation of treatment on institutional or cooperative-group protocols that specified CNS prophylaxis; availability of complete IT chemotherapy records (agent[s], dose, date), systemic therapy details, baseline CNS status, and follow-up data for CNS relapse and survival endpoints.

Patients were excluded if they had incomplete key data (missing IT dates or outcome documentation), received the majority of treatment off-site without verifiable records, had isolated CNS relapse at presentation without subsequent protocol-directed prophylaxis, or had concurrent conditions precluding lumbar puncture throughout induction and consolidation.

Data were abstracted from chemotherapy roadmaps, procedure notes, pharmacy logs, and laboratory systems by two independent reviewers using a standardized case report form. Variables captured included demographics, leukemia subtype and risk category, baseline CNS status, cytogenetics, MRD results, systemic high-dose methotrexate/cytarabine exposure, IT regimen and dates, cranial irradiation, infectious episodes, transfusion support, and outcomes. The primary exposure was the receipt and intensity of IT chemotherapy for CNS prophylaxis. IT regimens included methotrexate alone or triple IT (methotrexate, cytarabine, hydrocortisone) according to protocol and risk group. The primary outcome was CNS relapse-free survival (CNS-RFS), defined as time from diagnosis to first CNS relapse (isolated or combined), censoring at last follow-up or death. Relapse-free survival (any site), overall survival, treatment-related neurotoxicity (clinical seizures, leukoencephalopathy, or chemical arachnoiditis), and serious procedure-related complications within seven days of the lumbar puncture were secondary outcomes. Multivariable models adjusted for age, sex, leukemia subtype (ALL/AML), risk group, baseline CNS status, presenting leukocyte count, cytogenetic risk, MRD at end-of-induction, systemic CNS-penetrant chemotherapy (such as high-dose methotrexate), and cranial irradiation to reduce confounding by indication.

Data were analyzed using SPSS v26. Descriptive statistics summarized cohort characteristics. Group comparisons used chi-square tests for categorical variables and t-tests for continuous variables, as appropriate. CNS-RFS and overall survival were estimated with Kaplan–Meier curves and compared with log-rank tests. Two-sided $p < 0.05$ was considered statistically significant.

Results

Data were collected from 150 patients, including 118 with acute lymphoblastic leukemia (ALL) and 32 with acute myeloid leukemia (AML). The mean age for the overall cohort was 8.4 ± 4.1 years, with the ALL group averaging 8.2 ± 4.0 years and the AML group 9.1 ± 4.3 years. Age ranged from 1 to 18 years in ALL and from 1 to 17 years in AML. Males constituted 58.7% of the overall sample (59.3% in ALL, 56.3% in AML), while females comprised 41.3% (40.7% in ALL, 43.7% in AML). Most patients presented with CNS1 status at baseline (81.3% overall), with CNS2 seen in 10.7% and CNS3 in 8.0%, proportions that were similar between leukemia types. High-risk cytogenetic features were identified in 29.3% of the cohort, slightly higher in ALL (30.5%) than in AML (25.0%). Minimal residual disease (MRD) ≥ 0.01% at the end of induction occurred in 24.0% overall, with a nearly identical distribution between ALL (23.7%) and AML (25.0%). (Table 1)

Table 1. Baseline Demographic and Clinical Characteristics of Patients (N = 150)

Characteristic	Total (N=150)	ALL (n=118)	AML (n=32)
Mean age (years) ± SD	8.4 ± 4.1	8.2 ± 4.0	9.1 ± 4.3
Age range (years)	1–18	1–18	1–17
Male, n (%)	88 (58.7)	70 (59.3)	18 (56.3)
Female, n (%)	62 (41.3)	48 (40.7)	14 (43.7)
Baseline CNS status – CNS1, n (%)	122 (81.3)	96 (81.4)	26 (81.3)
Baseline CNS status – CNS2, n (%)	16 (10.7)	12 (10.2)	4 (12.5)
Baseline CNS status – CNS3, n (%)	12 (8.0)	10 (8.5)	2 (6.3)
High-risk cytogenetics, n (%)	44 (29.3)	36 (30.5)	8 (25.0)
MRD ≥ 0.01% at end of induction, n (%)	36 (24.0)	28 (23.7)	8 (25.0)

Across all patients, 41.3% received single-agent methotrexate (MTX) as IT therapy (38.9% in the full-intensity group and 47.6% in the reduced-intensity group). In comparison, 58.7% received triple IT therapy with methotrexate, cytarabine, and hydrocortisone (61.1% in full-intensity vs 52.4% in reduced-intensity). The median number of IT doses was higher in the full-intensity group at eight doses (IQR 7–9) compared to 5 doses (IQR 4–6) in the reduced-intensity group. By definition, all 108 patients in the full-intensity group achieved ≥ 90% of the planned IT intensity, whereas all 42 patients in the reduced-intensity group received < 90% of the planned IT regimen. (Table 2)

Table 2. Intrathecal Chemotherapy Delivery

Variable	Total (N=150)	Full-Intensity (n=108)	Reduced-Intensity (n=42)
IT regimen – Single-agent MTX, n (%)	62 (41.3)	42 (38.9)	20 (47.6)
IT regimen – Triple IT*, n (%)	88 (58.7)	66 (61.1)	22 (52.4)
Median IT doses (IQR)	—	8 (7–9)	5 (4–6)
IT intensity ≥ 90% planned, n (%)	—	108 (100.0)	—
IT intensity < 90% planned, n (%)	—	—	42 (100.0)

*Triple IT: methotrexate, cytarabine, hydrocortisone.

Any CNS relapse occurred in only 3.7% (n=4) of the full-intensity group, compared with 23.8% (n=10) in the reduced-intensity group, a statistically significant difference ($p<0.001$). Isolated CNS relapse was seen in 2.8% (n=3) of full-intensity recipients versus 14.3% (n=6) in the reduced group ($p=0.01$), while combined CNS plus systemic

relapse occurred in 0.9% (n=1) versus 9.5% (n=4), respectively (p=0.02). Among patients with baseline CNS2 or CNS3 status (n=28 in each group), relapse was significantly more common with reduced-intensity IT (35.7%, n=10) than with full-intensity IT (7.1%, n=2; p=0.01). (Table 3)

Table 3. CNS Relapse Outcomes by IT Intensity

Outcome	Full-Intensity (n=108)	Reduced-Intensity (n=42)	p-value
Any CNS relapse, n (%)	4 (3.7)	10 (23.8)	<0.001
Isolated CNS relapse, n (%)	3 (2.8)	6 (14.3)	0.01
Combined CNS + systemic relapse, n (%)	1 (0.9)	4 (9.5)	0.02
CNS relapse in CNS2/3 at baseline, n (%)	2/28 (7.1)	10/28 (35.7)	0.01

Five-year CNS relapse-free survival (CNS-RFS) was markedly higher in the full-intensity group at 96.0% compared to 71.4% in the reduced-intensity group (p<0.001). Similarly, five-year overall survival was 92.6% for full-intensity versus 78.5% for reduced-intensity IT (p=0.03). After adjusting for age, sex, leukemia type, risk group, baseline CNS status, MRD, and cranial irradiation, the hazard ratio for CNS relapse was 4.85 (95% CI: 1.78–13.21; p=0.002). (Table 4)

Table 4. Survival Outcomes

Outcome	Full-Intensity (n=108)	Reduced-Intensity (n=42)	p-value
5-year CNS-RFS (%)	96.0	71.4	<0.001
5-year Overall Survival (%)	92.6	78.5	0.03
HR for CNS relapse (adjusted)*	1.00 (ref)	4.85 (95% CI: 1.78–13.21)	0.002

*Adjusted for age, sex, leukemia type, risk group, baseline CNS status, MRD, and cranial irradiation.

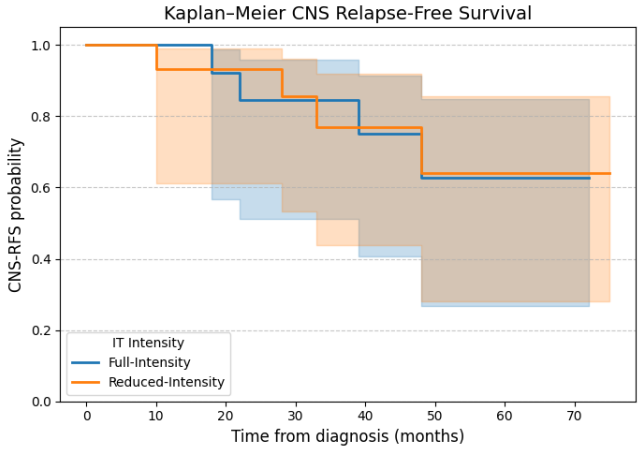

Figure 1 Kaplan-Meier CNS relapse-free survival.

Neurotoxicity of any type occurred in 7.3% (n=11) of patients, with chemical arachnoiditis in 3.3% (n=5), seizures in 2.7% (n=4), and leukoencephalopathy in 1.3% (n=2). Procedural complications, specifically traumatic lumbar puncture, occurred in 5.3% (n=8) of the total cohort. (Table 5)

Table 5. Treatment-Related Toxicity

Toxicity type	Total (N=150)	n (%)
Neurotoxicity (any)	11	7.3
– Chemical arachnoiditis	5	3.3
– Seizures	4	2.7
– Leukoencephalopathy	2	1.3
Procedural complications	8	5.3
– Traumatic lumbar puncture	8	5.3
Permanent neurologic deficit	0	0.0

Discussion

This study evaluated the impact of intrathecal (IT) chemotherapy intensity on central nervous system (CNS) relapse-free survival in pediatric patients with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). The results showed that receipt of 90% of the intended IT doses was firmly linked to meaningful minimization of CNS relapse rates down the road and enhanced long-term CNS relapse-free survival (CNS-RFS). This difference was considered clinically significant as only 3.7 percent CNS relapses were observed in the full-intensity group as

compared to 23.8 percent in the reduced-intensity group. These findings indicate the significance of standard delivery of protocol-determined prophylaxis to the CNS to present the best outcomes in pediatric leukemias (14). Full-intensity IT therapy appears to have a protective effect, which is consistent with both the historical data and current cooperative group trial data, which have demonstrated that the relapse in the CNS is <5% in standard-risk ALL done in free-of-charge chemotherapy using doses suitable to direct against the CNS without the necessity of normal practice cranial irradiation. Consistent with our observations, previous studies by Children Oncology Group and BFM Consortium reported that under-delivery of IT therapy regardless of its cause, toxicity, logistical or patient related, is associated with increased risk of a CNS relapse, especially in patients with high-risk characteristics at baseline, such as CNS2/CNS3 status b and elevated leukocyte count or T-cell phenotype. The difference was greatest in patients with CNS2/3 at diagnosis, in which there was a five-fold higher rate of relapse using reduced intensity prophylaxis (35.7% vs. 7.1%) (15).

Triple IT therapy (methotrexate, cytarabine, and hydrocortisone) incurs little estimation of overall benefit over single-agent methotrexate in the entire population; however, results revealed that it conferred a viable benefit in high-risk patients (16). This implies that although standard-risk CNS1 patients have demonstrated benefit with single-agent IT therapy in the presence of either systemic high-dose methotrexate or cytarabine, intensified IT regimens may be favorable in patients at greater baseline risk of central nervous system relapse. This subtlety supports the importance of risk-adjusted prophylaxis of the CNS and the need to avoid a blanket strategy. A neurotoxicity percentage of 7.3 in patients has been observed, with a majority being reversible (17). The most common one was chemical arachnoiditis; seizures and leukoencephalopathy were also observed. These rates agree with other reported ranges of 5 to 10 percent of the IT-related neurotoxicity in the pediatric patient population. Procedural complications that did not lead to permanent deficits were noted in 5.3 percent of patients and included traumatic lumbar puncture. This highlights the fact that when done in the ideal conditions using skilled personnel and sufficient supportive treatment, IT chemotherapy still constitutes a low risk, albeit a part, of pediatric leukemia treatment (18).

Another interesting finding was that nearly 10% of reduced-intensity cases were related to logistical or administrative delays as opposed to medical contraindications. These unnecessary disruptions may cumulatively negatively affect outcomes, especially in resource-scarce environments (19). This brings out a crucial systems-level implication: chemotherapy intensity not only requires care of a clinical management system but also of the institutional maintenance, the availability of drugs, and the success of scheduling operations. The decrease in cranial irradiation, seen in current pediatric regimens, has increased our dependence on sole chemotherapy for CNS prophylaxis (20). Although this method reduces the late effects, which include neurocognitive impairments, endocrinopathies, and second malignancies, it places more stress on consistent implementation of the intended schedule regarding the IT and systemic CNS-specific chemotherapy pattern. Our results support the statement that IT prophylaxis with full intensity becomes particularly vital in cases with the exclusion of cranial irradiation, to avoid CNS relapse. Nevertheless, some limitations have to be considered. Retrospective design creates the possibility of selection bias and unmeasured confounding. Also, although our sample was adequate to reveal statistically significant differences in CNS relapse rates, it may not have allowed us to adjust for the power to detect smaller differences among IT regimens in some subgroups.

Conclusion

It is concluded that maintaining full-intensity intrathecal chemotherapy is a critical factor in reducing central nervous system relapse and improving long-term CNS relapse-free survival in pediatric patients with acute lymphoblastic leukemia and acute myeloid leukemia. Patients who received ≥90% of planned IT doses had markedly lower relapse rates compared to those with reduced-intensity schedules, with the benefit most pronounced in high-risk subgroups such as those with CNS2/3 status at diagnosis. While the overall safety profile of IT therapy was favorable, a notable proportion of treatment interruptions were due to avoidable logistical factors, underscoring the need for system-level improvements to ensure timely delivery.

Declarations

Data Availability statement

All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department concerned. (IRBEC-24)

Consent for publication

Approved

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Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

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MJ (Fellow),
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All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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