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Review Article

Central Nervous System Involvement at Diagnosis in Infants with Acute Lymphoblastic Leukemia (ALL): Incidence and Outcome

Camille Bertrand[1*], Lukas Kramer[2] and Nikos Andreadis[3]

[1]Department of Haematology, Sorbonne University, Paris, France

[2]Department of Immunotherapy, Charite University Medicine Berlin, Berlin, Germany

[3]Department of Clinical Trials, National and Kapodistrian University of Athens, Athens, Greece

***Address for Correspondence:** Camille Bertrand, Department of Haematology, Sorbonne University, Paris, France

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Summary

Infants under one year with acute lymphoblastic leukaemia present with central nervous system disease three to five times more often than older children, and it identifies a group whose event-free survival is roughly half that of their central nervous system-negative peers. The newest and most effective therapy for these infants may not reach that compartment at all.

Objectives: To review the published evidence on central nervous system involvement at diagnosis in infant acute lymphoblastic leukaemia: how often it occurs, how it relates to KMT2A rearrangement and age, what it predicts for relapse and survival, and how the compartment has responded to successive treatment strategies.

Material and Methods: Narrative review of international cooperative group trials, registry analyses and correlative studies indexed in PubMed and the major haematology and oncology journals. Studies were eligible if they reported the frequency or outcome of central nervous system disease in a defined infant leukaemia population, or the effect of a treatment strategy on central nervous system relapse. No new patient data were generated and no patients were recruited; every estimate quoted is one published by the original investigators.

Results: Central nervous system involvement was present in 13.8 per cent of infants at diagnosis in the largest international trial, against 2 to 5 per cent in children over one year. Among 139 infants with recorded status, 28 of 50 with central nervous system disease relapsed, giving event-free survival of 0.27 and cumulative relapse incidence of 0.65, against 21 relapses among 89 without involvement, event-free survival 0.58 and relapse incidence 0.26 ($p < 0.001$ for both). Of 213 relapses occurring after first remission in 442 patients, 24 per cent involved the central nervous system, comprising 11 per cent isolated and 13 per cent combined marrow and central nervous system disease. Adding one course of a CD19-directed bispecific antibody to the same chemotherapy backbone raised two-year disease-free survival from 49.4 to 81.6 per cent, yet every relapse that occurred involved the central nervous system.

Conclusion: Central nervous system disease at diagnosis is common in infants, strongly prognostic, and has proved the least tractable compartment to successive therapeutic advances. That the most effective new agent leaves relapses concentrated there is an argument for intensifying intrathecal rather than systemic therapy alongside it.

Abbreviations: ALL – Acute Lymphoblastic Leukaemia, CNS – Central Nervous System, KMT2A-r – KMT2A-Rearranged, KMT2A-g – KMT2A-Germline, EFS – Event-Free Survival, DFS – Disease-Free Survival, OS – Overall Survival, CIR – Cumulative Incidence of Relapse, CR1 – First Complete Remission, MRD – Minimal Residual Disease, HSCT – Haematopoietic Stem Cell Transplantation, WBC – White Blood Cell Count.

Keywords: *Infant Leukaemia; Acute Lymphoblastic Leukaemia; Central Nervous System; KMT2A Rearrangement; Interfant*

Introduction

Acute lymphoblastic leukaemia diagnosed under one year of age is a different disease from the same diagnosis made at five. It is rare, at around 1.8 cases per hundred thousand and under 5 per cent of paediatric acute lymphoblastic leukaemia [1,2], and it is dominated by rearrangement of the KMT2A gene, present in roughly three quarters of cases in the largest trial cohort [3,4].

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That genetic distinction drives everything else. KMT2A-rearranged infant disease carries five-year event-free survival below 40 per cent against above 75 per cent for germline cases [5,6,7], relapses occur early, with two thirds within one year and 90 per cent within two years of diagnosis [8], and outcomes have not improved across successive intensifications of conventional chemotherapy [3,8].

Central nervous system disease sits at the centre of this picture and is often treated as a secondary observation. Infants present with it several times more often than older children, and it is one of the clinical features that partitions outcome within genetic subtypes [9]. Successive cooperative group protocols have addressed the compartment with intrathecal chemotherapy and systemically active agents rather than cranial irradiation, which is avoided in this age group [4,10].

This review sets out how often central nervous system disease is present at diagnosis, what it predicts, and why it has proved the compartment most resistant to the therapeutic gains of the past two decades.

Material and Methods

Search strategy: PubMed and the archives of the major haematology and paediatric oncology journals were searched for studies of central nervous system disease in infant leukaemia. Search terms combined infant acute lymphoblastic leukaemia with central nervous system involvement, CNS leukaemia, KMT2A, MLL rearrangement, Interfant, relapse and intrathecal therapy. Reference lists of retrieved trials and reviews were screened by hand.

Eligibility: Studies were included if they reported the frequency or clinical significance of central nervous system disease in a defined infant leukaemia population, outcomes stratified by central nervous system status, or the effect of a treatment strategy on central nervous system relapse. Studies in older children and adults are cited where they provide the comparator and are identified as such.

Data extraction and handling: Design, cohort size, protocol, definition of central nervous system involvement and reported frequencies or survival estimates were extracted as published. Whether a figure refers to involvement at diagnosis or at relapse is stated throughout, and isolated central nervous system relapse is distinguished from combined marrow and central nervous system relapse, because the two carry different implications. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 4 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

How often infants present with central nervous system disease: In the largest international trial for this population, central nervous system involvement was recorded in 13.8 per cent of infants at diagnosis [4,10]. The comparison that gives this figure meaning is with older children, in whom central nervous system involvement at diagnosis runs at 2 to 5 per cent (Figure 1) [10]. Infants therefore present with central nervous system disease roughly three to five times as often.

Involvement is not evenly distributed within the infant group. It is commonest below six months of age [11], and it is more frequent in KMT2A-rearranged than in germline disease [10,12]. Analysis of a North American infant trial found that age, white cell count, sex and central nervous system disease are unevenly distributed across KMT2A partner gene subtypes and, in univariate analysis, partition event-free survival within those subtypes [9]. Central nervous system status is therefore entangled with the genetic and demographic features that already define risk, which complicates any attempt to weigh its independent contribution.

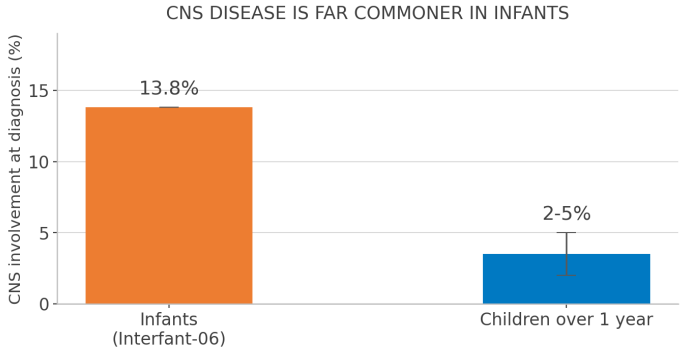

Figure 1: Central nervous system involvement at diagnosis in infants against children over one year [4,10]

What it predicts: The prognostic signal is large. Among infants with recorded central nervous system status, 28 of 50 with involvement relapsed, giving event-free survival of 0.27 and a cumulative incidence of relapse of 0.65. Among 89 without involvement, 21 relapsed, giving event-free survival of 0.58 and cumulative relapse incidence of 0.26, with $p < 0.001$ for both comparisons (Figure 2) [11].

Roughly halving event-free survival places central nervous system status alongside the established risk factors used for stratification. In the predecessor trial, infants carrying the full combination of adverse features, age under six months, poor prednisolone response and white cell count above 300 x 10^9/L, had four-year event-free survival of 20 per cent against 45 per cent for others [3,5]. Central nervous system involvement has been described as a high-risk feature in KMT2A-rearranged infant disease on that basis [10,13].

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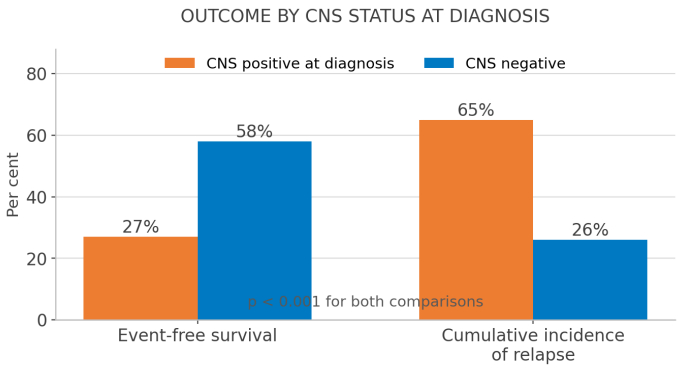

Figure 2: Event-free survival and cumulative relapse incidence by central nervous system status at diagnosis [11]

Study	Cohort	Focus	Principal reported finding
Nagayama et al. 2006 [7]	Japanese	KMT2A-germline	Germline disease highly curable with chemotherapy alone
Hilden et al. 2006 [14]	CCG 1953	Prognostic factors	Prognostic factor analysis in infant disease
Pieters et al. 2007 [3]	Interfant-99	Protocol	Four-year EFS 20% with all adverse features
Mann et al. 2010 [15]	Interfant-99	Transplant	Benefit confined to a poor-prognosis subgroup
Pieters et al. 2019 [4]	Interfant-06	Protocol	651 patients; CNS involvement 13.8% at diagnosis
van der Sluis et al. 2023 [8]	30 infants	Blinatumomab	2-year DFS 81.6%; all relapses involved the CNS

Table 1: Principal studies reviewed, with cohort and the finding as reported by the original investigators

Where infants relapse: Of 442 patients reaching first complete remission in the largest trial, 213 relapsed, and 50 of those relapses, 24 per cent, involved the central nervous system: 11 per cent isolated central nervous system disease and 13 per cent combined marrow and central nervous system disease (Figure 3) [4,10].

The proportion of relapses involving the central nervous system is not higher than in older children, where comparable series report 20 to 28 per cent [10]. What differs is the absolute burden. Because infants relapse so much more often overall, central nervous system relapse affected 50 of 442 patients, 11 per cent of the whole cohort, against 1 to 2 per cent in childhood acute lymphoblastic leukaemia [10]. A proportion that looks unremarkable therefore describes an absolute risk five to ten times higher.

In germline disease treated on the same protocol the pattern persists in milder form. Among 31 relapses, 19.4 per cent were isolated central nervous system and 16.1 per cent combined marrow and central nervous system, against 48.4 per cent isolated marrow, with six-year event-free and overall survival of 73.9 and 87.2 per cent [11,16]. Central nervous system disease is therefore not confined to the KMT2A-rearranged group, although it is commoner there.

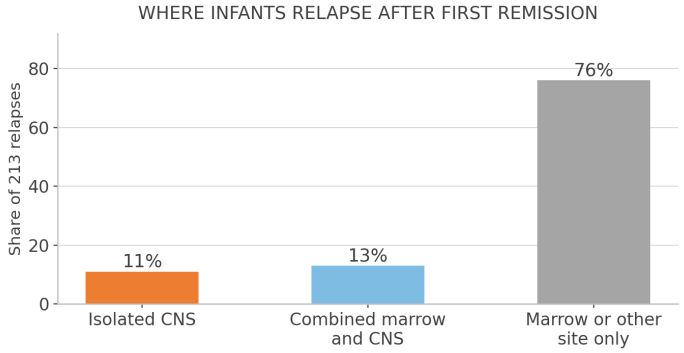

Figure 3: Site of relapse among 213 infants relapsing after first complete remission [4,10]

The compartment that immunotherapy did not reach: The most important recent development in this disease is the addition of a single post-induction course of the CD19-directed bispecific antibody blinatumomab to the existing chemotherapy backbone. In 30 infants with newly diagnosed KMT2A-rearranged disease enrolled across nine countries, two-year disease-free survival was 81.6 per cent (95% CI 60.8-92.0) against 49.4 per cent (95% CI 42.5-56.0) in matched historical controls from the parent trial, and two-year overall survival 93.3 per cent against 65.8 per cent (Figure 4) [8,17].

That is the largest single improvement reported in this disease in decades. The observation relevant to this review is what happened in the few patients who did relapse: every one of them had central nervous system involvement at relapse. The investigators drew the obvious inference, that adequate intrathecal chemotherapy is needed during the blinatumomab infusion because the agent's efficacy against central nervous system leukaemia may be limited [8].

A bispecific antibody that recruits circulating T cells to CD19-positive blasts depends on both cell types reaching the target. Neither traverses the blood-brain barrier freely, so a systemic agent that clears the marrow efficiently may leave a sanctuary site untreated. If confirmed in the larger successor trial, this would mean the therapy that most improved overall outcome simultaneously concentrated the residual failures into one compartment [8,18].

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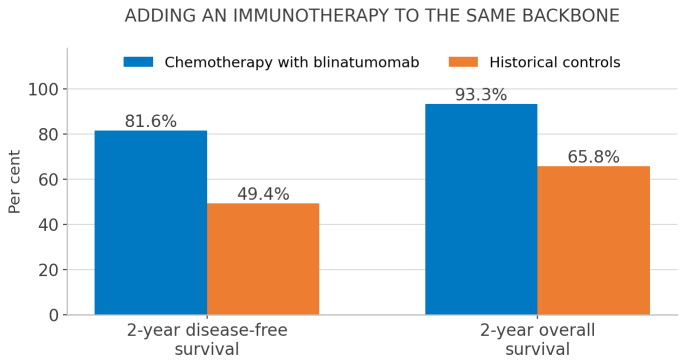

Figure 4: Outcome with the addition of one course of blinatumomab against historical controls on the same backbone [8]

Measure	Infants	Children over 1 year
CNS involvement at diagnosis	13.8%	2-5% [4,10]
Relapses involving the CNS	24%	20-28% [10]
CNS relapse as share of whole cohort	11%	1-2% [10]
Five-year EFS, KMT2A-rearranged	Below 40%	Not applicable [5,6]

Table 2: Central nervous system disease in infants against older children with acute lymphoblastic leukaemia

How the compartment is currently treated: Cranial irradiation is avoided in infants because of its effect on the developing brain, so central nervous system-directed therapy rests on intrathecal chemotherapy combined with systemically active agents such as high-dose methotrexate and cytarabine [4,10]. Successive protocols have adjusted the number and timing of intrathecal doses rather than introducing a fundamentally new approach.

Transplantation has been examined as an alternative intensification. In the predecessor trial, allogeneic transplantation improved outcome only within a defined poor-prognosis subgroup rather than across infants generally [15], and minimal residual disease measurement has since become the principal tool for identifying who might benefit [19,20]. Neither approach addresses the central nervous system compartment specifically.

Targeted agents have been tried without changing the picture. A FLT3 inhibitor added to chemotherapy in newly diagnosed KMT2A-rearranged infant disease did not deliver the expected benefit [21], and germline cases treated with chemotherapy alone achieved outstanding outcomes in a separate cohort, confirming that the problem is specific to the rearranged group [22]. Recurrent genetic fusions have since been described that redefine the germline category itself [23].

How central nervous system status is defined, and why it matters: The figures above rest on a classification that is less firm than it appears. Involvement is graded by cell count and cytomorphology on cerebrospinal fluid, with CNS1 denoting no blasts, CNS2 fewer than five white cells per microlitre with blasts present, and CNS3 five or more with blasts. Protocols have differed in whether CNS2 is treated as involvement, and in how a traumatic lumbar puncture with blasts is handled [4,14].

This is not a technicality. A reported frequency of 13.8 per cent depends on where that boundary is drawn, and comparisons between eras or between cooperative groups can reflect definitional differences as much as biological ones [4,11,14]. Infants compound the problem: obtaining an adequate, atraumatic sample from a child weighing a few kilograms is harder than in an older child, and cell counts are interpreted against age-specific normal ranges that are themselves wider.

Flow cytometry detects blasts in cerebrospinal fluid more sensitively than cytomorphology but has not been incorporated into the risk stratification these protocols use [4,10].

Feature	Reported association	Source
Age under 6 months	Highest frequency of CNS involvement	Interfant cohorts [11]
KMT2A rearrangement	More frequent CNS disease than germline	Interfant and COG analyses [9,10]
High white cell count	Travels with CNS involvement	COG P9407 partner gene study [9]
KMT2A partner gene	Uneven distribution of CNS disease across subtypes	COG P9407 partner gene study [9]
CD19-directed immunotherapy	All observed relapses involved the CNS	Blinatumomab phase 2 [8]

Table 3: Features reported to associate with central nervous system disease in infant acute lymphoblastic leukaemia

The cost of treating the compartment: Central nervous system-directed therapy in infants is constrained by the age of the patient rather than by efficacy. Cranial irradiation would be effective and is not used, because the developing brain in the first year of life is the most radiosensitive tissue in paediatric oncology [4,10]. Intrathecal chemotherapy and high-dose systemic agents are what remain, and both carry their own neurotoxicity in this age group.

Long-term follow-up of survivors is therefore part of the calculus. A study of survivors of infant disease documented the late effects that follow intensive therapy delivered in the first year of life [24], and these are the patients in whom any intensification of central nervous system-directed treatment would be borne. The trade-off is unusually sharp here: relapse in this compartment is very often fatal, while prophylaxis against it is delivered to a brain undergoing its most rapid period of development.

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Discussion

Three findings interlock. Central nervous system involvement is three to five times commoner in infants than in older children [4,10]. It roughly halves event-free survival, from 0.58 to 0.27 [11]. And it accounts for a share of relapses that looks ordinary in percentage terms but represents an absolute risk five to ten times that of childhood disease, because the total relapse rate is so much higher [10].

Set against that, the therapeutic history is one of systemic intensification. Chemotherapy blocks borrowed from myeloid protocols, transplantation, FLT3 inhibition and now bispecific antibody therapy have all been directed at the marrow, while central nervous system-directed treatment has remained essentially intrathecal methotrexate and cytarabine throughout [3,4,15,21]. The compartment has been managed rather than targeted.

Why the blinatumomab result matters most here

The finding that every relapse in the blinatumomab cohort involved the central nervous system deserves more attention than it usually receives [8]. With only a small number of events the observation could be chance, and it must be read with that caution. But it is mechanistically plausible: a bispecific antibody depends on effector T cells and target blasts meeting, and the central nervous system is a compartment neither reaches readily [8,18].

If it holds, the implication is specific rather than general. It would not argue against the therapy, whose overall effect is the largest reported in this disease, but it would mean that intrathecal intensity should be maintained or increased alongside it rather than reduced in response to improved systemic control. The successor phase III trial is the setting in which this will be resolved [8].

Interpreting the prognostic figures

The comparison of 0.27 against 0.58 event-free survival is univariate, and central nervous system status travels with age under six months, higher white cell count and KMT2A rearrangement, all of which independently worsen outcome [9,11]. Part of the apparent effect is therefore shared with those variables rather than attributable to central nervous system disease alone.

Whether that matters depends on the purpose. For prognostication the univariate figure is what a clinician sees, and it is accurate. For deciding whether to intensify central nervous system-directed therapy specifically, the independent contribution is what matters, and no study reviewed here isolates it convincingly [9,11].

Study limitations

The limitations belong to the underlying literature. Infant acute lymphoblastic leukaemia is rare, so even international trials accrue several hundred patients over many years and subgroup analyses rest on small numbers [3,4]. Definitions of central nervous system involvement have varied between protocols and eras, particularly in how CNS2 status and traumatic lumbar punctures are handled, which affects reported frequency [4,14]. Central nervous system status is confounded with age, white cell count and genetic subtype, and multivariable analyses isolating it are lacking [9]. The blinatumomab data derive from 30 patients compared against historical rather than concurrent controls [8]. And several informative cohorts predate current molecular classification, so the populations are not strictly comparable across the period [7,14,23].

Two gaps deserve naming. No trial has randomised central nervous system-directed intensity in infants, so current intrathecal schedules rest on convention and extrapolation rather than comparative evidence [4,10]. And no study reports long-term neurocognitive outcome stratified by central nervous system status at diagnosis, although late effects in survivors of infant disease have been characterised in general terms [24,25].

Conclusion

Central nervous system disease is present at diagnosis in 13.8 per cent of infants with acute lymphoblastic leukaemia, three to five times the rate in older children, and it roughly halves event-free survival from 0.58 to 0.27. Relapses involving the central nervous system make up 24 per cent of all relapses, which is unremarkable proportionally but represents 11 per cent of the entire cohort against 1 to 2 per cent in childhood disease. Two decades of therapeutic development have intensified systemic treatment while central nervous system-directed therapy has remained largely unchanged, and the most effective new agent left every observed relapse confined to that compartment. The next advance in this disease is more likely to come from targeting the central nervous system than from further systemic intensification.

Acknowledgements

Trials in a disease this rare depend on decades of accrual across many countries, and that effort underlies everything reported here.

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The review was unfunded. No research council, manufacturer or foundation was approached for support, and none was received.

Conflict of Interest

No author has ties to any manufacturer of the agents discussed.

Ethics Statement

Nothing in this review required access to a patient. It rests on trials and registries that are already reported in the literature, so no ethics

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committee submission arose.

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