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DOI:
10.1182/bloodadvances.2023011267

blood advances

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Tracking no: ADV-2023-011267R1

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Abstract:

Conflict of interest: No COI declared

COI notes:

Preprint server: No;

Author contributions and disclosures: D.O.C. and A.V. wrote the first and subsequent drafts of the manuscript; and all authors contributed to the acquisition or analysis of data, critically revised the manuscript, approved the final version for publication, and agreed to be accountable for the results published.

Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: Data sharing should be discussed with the corresponding suthor.

Clinical trial registration information (if any): UKALL2003: ISRCTN number 07355119 UKALL2011: ISRCTN number 64515327

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To the Editor:

Despite significant improvements in therapy, outcomes for childhood and young persons (CYP) T-cell acute lymphoblastic leukemia (T-ALL) remain inferior to those in B-ALL.[1] The aggressive nature of T-ALL is illustrated by the increased incidence of central nervous system (CNS) infiltration at diagnosis, typically identified through the presence of leukemic blasts in the cerebrospinal fluid (CSF), which predicts an increased risk of subsequent CNS relapse.[2] Historically, CNS-directed therapy consisted of prophylactic cranial radiotherapy (CRT). However, due to the significant burden of toxicity, several consortia now either omit CRT altogether or limit its use to specific subgroups, instead utilising intrathecal chemotherapy.[3–5]

In a recent issue of Blood, the Children's Oncology Group reported the impact of CNS status on outcome in an impressive cohort of 2164 patients treated on the AALL0434 and AALL1231 trials, showing a worse outcome for patients with CNS-3 status at diagnosis.[6] Importantly, while AALL0434 delivered CRT to over 90% of patients, AALL1231 limited it to the 10% of patients with CNS-3 or very high risk disease. Despite this change in practice for patients with CNS-1 or CNS-2, outcomes were comparable across the two trials, indicating that omission of CRT had no significant impact on outcome, supporting the decision to remove CRT in these groups.

Notably, other consortia including the UK, St. Jude Children's Research Hospital and the Dutch Childhood Oncology Group have gone a step further, eliminating CRT in the front line treatment of all patients with T-ALL, including those with CNS-3.[7–10] As the COG trials

delivered CRT to all patients with CNS-3, the authors were unable to assess the impact of CRT in this group, meaning the benefit of CRT in CNS-3 remains unanswered. To address this, we have reviewed the outcomes of the 665 patients treated for T-ALL on the analogous UK National Cancer Research Institute (NCRI) trials, UKALL2003 and UKALL2011, which ran concurrently with the COG trials and eliminated CRT for patients with CNS-3 disease. UKALL2003 was approved by the Scottish Multi-Centre Research Ethics Committee. UKAL2011 was approved by the North Thames Research Ethics Committee. The studies were conducted according to the Declaration of Helsinki.

Both UKALL2003 and UKALL2011 recruited patients aged 1-24 and have been previously reported.[4,5,11,12] Briefly, treatment comprised a dexamethasone-based backbone that included a 4-drug induction, BFM consolidation, interim maintenance, delayed intensification (DI) and maintenance therapy. Stratification was based on morphological early response and end of induction MRD. UKALL2003 randomizations found improved outcome for escalated treatment, including Capizzi-style methotrexate (C-MTX), for MRD positive patients,[5] and found no impact of omitting one of the two DI blocks in low risk patients.[4] UKALL2011 randomizations identified no impact of a shorter dexamethasone course in induction,[11] the addition of high-dose methotrexate (HD-MTX), or the removal of dexamethasone-vincristine pulses in maintenance.[12] While UKALL2003 initially recommended CRT for patients with CNS-3, this was eliminated from 2009 onwards, after which CNS-directed therapy comprised intrathecal methotrexate at regular intervals throughout treatment; UKALL2003 recommended additional weekly intrathecal methotrexate throughout induction for patients with CNS-3 while UKALL2011 recommended for both CNS-2 and CNS-3. CNS status was assessed by a combination of cell count (manual

or automated) and cytospin using standard definitions (CNS-1: ≤5 WBCs/μL, CNS-2: ≤5 WBCs/μL with cells present on cytospin, CNS3: >5 WBCs/μL).

In total, 637 patients with T-ALL had CNS status available. There were 557 patients with CNS-1 (87.4%), 44 with CNS-2 (6.9%) and 36 with CNS-3 (5.7%). Eight patients with CNS-3 recruited prior to 2009 who received CRT were excluded from further analyses. While the proportion of patients with CNS-3 is comparable to the COG studies (5.7% vs. 7.0%), there were significantly fewer CNS-2 patients (6.9% vs. 20.4%) and significantly more CNS-1 patients (87.4% vs. 72.3%) in the UK cohort ($p<0.001$). This is unsurprising given the very wide variation in the rates of CNS-2 reported between different trial groups, which is thought to be due to variability in methodological and analytical practices rather than a true clinical difference.[13]

Kaplan-Meier plots showing cumulative incidence of relapse (CIR), event-free survival (EFS) and overall survival (OS) for patients treated on UKALL2003 and UKALL2011 split by CNS status are shown in Figure 1. Comparison of the 4-yr survival rates based on CNS status are shown for the UKALL and COG cohorts in Table 1. Most importantly, outcomes are not significantly different for the CNS-3 patients, despite omission of CRT in the UK cohort. Although there is a slightly higher relapse rate in UK patients with CNS-3, this did not translate into poorer long-term survival. This is in keeping with a meta-analysis of over 16,000 patients with predominantly B-ALL that concluded CRT reduced the risk of isolated and combined CNS relapse in patients with CNS-3 but had no impact on EFS and OS.[14] As with the COG data, patients with CNS-3 on the UKALL trials had an increased risk of isolated CNS relapse(CNS1 – 3%, CNS-2 – 9%, CNS-3 – 14%, $p=0.005$).

Outcomes for patients with CNS-1 were comparable across the two cohorts. In contrast, outcomes for CNS-2 patients were worse in the UK cohort with double the relapse rate and lower EFS and OS. This may, in part, be related to the lower proportion of patients with CNS-2 in the UK cohort. It is possible that the methodology used in the UK is less sensitive than that used by COG, meaning that patients labelled as CNS-2 have a higher burden of disease, more similar to CNS-3 status, whilst patients with lower level disease, who COG would diagnose as CNS-2, are diagnosed as CNS-1 in the UK. Importantly, this means that the COG's finding that CNS-2 status does not affect outcome may not be generalizable to other trial groups. Going forward, given the poor reproducibility of microscopy across individual labs and trial consortia, further research is needed to develop more sensitive biomarkers for the accurate detection of CSF disease that can be used to assess initial burden and response to therapy. Recently, multicolour flow cytometric analysis has been shown to provide more sensitive analysis of CSF;[15,16] an international study to assess the clinical utility of routine flow cytometric analysis of CSF samples is currently underway as part of the European ALLTogether Trial (NCT03911128).

Overall, comparison of these cohorts provides a strong indication that CRT provides minimal benefit to patients with CNS-3 disease at diagnosis. Given the high rates of neurocognitive impairment and secondary CNS malignancies,[17–19] we believe strong consideration should be given to eliminating CRT in first line treatment for all patients with T-ALL. We note that COG AALL0434 showed a remarkable benefit for nelarabine in the CNS-3 group with a 4-yr DFS of 93.1% ± 5.2% with nelarabine vs 70.2% ± 5.8% without.[20] Although these patients also

received CRT, and numbers are small, the improvement is impressive and raises the question of whether nelarabine would have a similar beneficial effect in the absence of CRT.

Authorship

Contribution: D.O.C. and A.V. wrote the first and subsequent drafts of the manuscript; and all authors contributed to the acquisition or analysis of data, critically revised the manuscript, approved the final version for publication, and agreed to be accountable for the results published.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Acknowledgements

D.O'C. is funded by a Cancer Research UK Clinician Scientist Fellowship (A27177). A.V.M. received funding from Blood Cancer UK (15036).

We would like to thank all the patients who took part in the UKALL trials as well as their families. UKALL2003 was supported by grants from Blood Cancer UK (previously Leukaemia and Lymphoma Research) and the Medical Research Council. UKALL2011 was funded by Cancer Research UK (CRUK). Delivery of both trials was supported by the UK National Cancer Research Institute (UK NCRI).

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Figure Legends

Figure 1. Kaplan-Meier plots showing A) CIR, B) EFS, C) OS split by CNS status for patients with T-ALL treated on UKALL2003 and UKALL2011

Tables

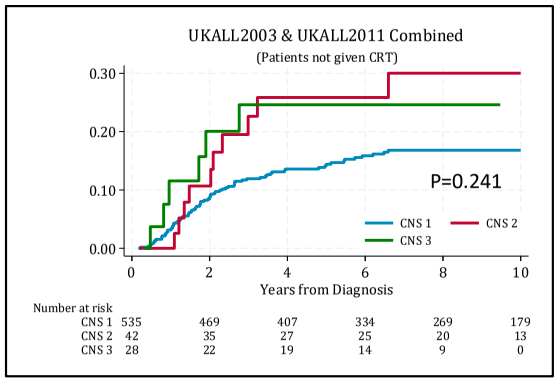
		CNS-1	CNS-2	CNS-3	P value*
UKALL2003/UKALL2011	**Proportion**	87.4%	6.9%	5.7%	
	4-yr CIR	13.6% ± 1.7%	25.9% ± 8.6%	24.6% ± 10.1%	0.241
	4-yr EFS	82.9% ± 1.6%	74.1% ± 6.7%	77.8% ± 8.0%	0.623
	4-yr OS	88.6% ± 1.4%	80.9% ± 6.1%	91.8% ± 5.6%	0.453
COG AALL0434/AALL1231	**Proportion**	72.3%	20.4%	7.3%	
	4-yr CIR	7.6% ± 0.7%	9.9% ± 1.4%	17.9% ± 3.1%	0.0002
	4-yr EFS	85.1% ± 1.0%	83.2 ± 2.0	71.8% ± 4.0%	0.0004
	4-yr OS	90.1% ± 0.8%	90.5% ± 1.6%	82.7% ± 3.4%	0.005
Survival rates are presented as rates ± standard errors; *1-sided log-rank test. CIR - Cumulative incidence of relapse; EFS - Event-free survival; OS - Overall survival; CNS - Central nervous system.					

Table 1. Comparison of outcomes between patients treated on UKALL2003/UKALL2011 and COG AALL0434/AALL1231

CIR, Cumulative incidence of relapse; EFS, Event-free survival; OS, Overall survival; CNS, Central nervous system.

Figure 1

A



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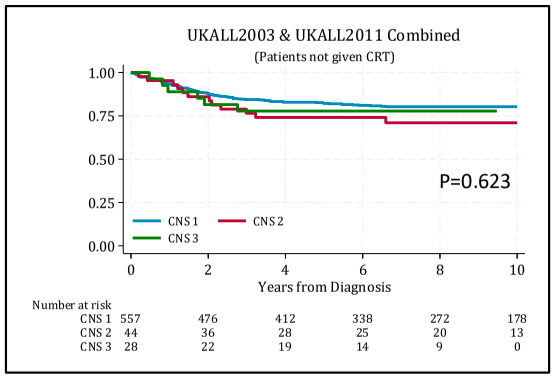

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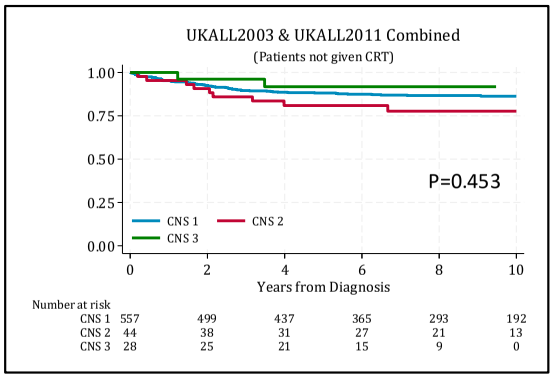

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