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Excellent outcomes in children and adolescents with CNS+ Burkitt lymphoma or other mature B-NHL using only intrathecal and systemic chemoimmunotherapy: results from FAB/LMB96 and COG ANHL01P1

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Authorship statement

MSC, HW, SG, and CP conceived and designed the study. LH, SG, CP, and MSC acquired the data. MSC, JRA, AB, KJL, PG, SLP, AA, CRP, TGG, JM GL, HW, BS, MB, and JKF interpreted the results. All authors reviewed, drafted or revised the manuscript and approved the final version for submission.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article. Data S1. Supplementary materials.

Conflict of Interest statement

Mitchell Cairo, MD is a consultant for Jazz Pharmaceuticals; Paul Galardy, MD received funding from Mission Therapeutics and has a financial interest in Abbott Laboratory.

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Burkitt lymphoma (BL) is the most common Non-Hodgkin lymphoma (NHL) in children, representing 40–50% of paediatric NHL (Cairo *et al,* 2012). BL is frequently advanced, involving the bone marrow (BM), central nervous system (CNS) or both, which requires aggressive therapy. BL is also the most frequently CNS-positive (CNS^+) paediatric NHL (9–13% of cases) (Cairo *et al,* 2007, 2012; Patte *et al,* 2007; Gerrard *et al,* 2008). Trials have strived to improve outcomes in CNS^+ BL and other mature B cell NHL (B-NHL), where prognoses are inferior (Salzburg *et al,* 2007). Specifically, CNS^+ patients who were also BM-positive (BM^+) had the worst outcomes on the French-American-British (FAB)/Lymphome Malins B (LMB)96 trial (Cairo *et al,* 2012). Yet most patients do achieve long-term survival, so studies also aim to reduce therapy-induced sequelae. The international FAB/LMB96 cooperative group trial previously demonstrated that CNS^+ B-NHL patients treated with intensified CNS-directed systemic and intrathecal (IT) therapies had similar event-free and overall survival (EFS, OS) to prior CNS radiotherapy-containing regimens (Cairo *et al*, 2007). Besides altering CNS-directed treatment, FAB/LMB96 also randomized standard-*versus* reduced-intensity arms: reduced-intensity was proven inferior (72% vs. 84% EFS) (Cairo *et al,* 2007). Here, we focus CNS^+ patients treated on the standard FAB/LMB96 C_1-arm.

Rituximab has proven beneficial in adult B-NHL, so shortly after FAB/LMB96, we investigated adding rituximab to the C_1-regimen in the Children's Oncology Group (COG)-ANHL01P1 trial (Goldman *et al,* 2014). Here, we present high-risk CNS^+ patient data from both the FAB/LMB96 C_1-arm and C0G-ANHL01P1 and compare them to prior LMB89 results. Overall, excellent EFS and OS were achieved, with further improvement with rituximab. Clinical trial information and approvals, CNS^+-defining criteria, chemotherapy details and statistical methods are listed in Data S1.

Forty-four CNS^+ mature B-NHL patients were treated on FAB/LMB96-C_1 (Cairo *et al,* 2007), with 84% having BL or BL-like histology and 52% dually CNS^+/BM^+. Fifteen COG-ANHL01P1 patients were CNS^+, 100% with BL and 53% CNS^+/BM^+. Thus, these results pertain to BL, because 88% of patients shared this pathological diagnosis ($P = 0.45$). No significant differences in age, gender, or BM/CNS status were seen between the patient groups (Table I and data not shown), with both cohorts mostly male (83%) and aged ≤14 years (88%). The types of CNS^+ patients on both trials were also similar, with 55% (FAB/LMB96-C_1) vs. 53% (COG-ANHL01P1) cerebrospinal fluid-positive (CSF^+), 36% vs. 33%

isolated CSF^+, and 36% vs. 33% dually BM^+/CSF^+. Each group also contained ~13% of patients with isolated cranial nerve palsies.

After correcting for the inferior arm of the FAB/LMB96 CNS^+ patients, estimated 4-year EFS was 75 ± 4.5% (FAB/LMB96-C_1; Table II); *versus* 93.3% on COG-ANHL01P1, with EFS in BM^+/CNS^+ and BM^+/CSF^+ subgroups likewise similar (data not shown). Overall, both trials illustrate that children, adolescents and young adults with high-risk CNS^+ mature B-NHL have outstanding outcomes when CNS radiation is replaced with CNS-directed systemic and IT chemotherapy (Cairo *et al,* 2007; Goldman *et al,* 2014). Prior studies like LMB89 used similar regimens, but with cranial radiation in CNS^+ patients. These results in CNS^+ patients show that CNS-directed systemic (high dose methotrexate, high dose cytarabine) and IT therapy (13 doses) can limit neurotoxicity by eliminating irradiation, yet still offer superior EFS and OS.

The COG-ANHL01P1 study added rituximab to therapy that was almost identical to FAB/LMB96-C_1, but reduced the doxorubicin infusion time. Despite an estimated 20% improvement in 4-year EFS in CNS^+ patients on COG-ANHL01P1 versus FAB/LMB96, this was not statistically significant due to the small sample size of COG-ANHL01P1. However, directly comparing these trials is complex, because these studies had key differences: (i) FAB/LMB96 randomized patients after the cytoreduction and induction cycles, thus excluding refractory/progressing patients and those who died of toxicity prior to randomization. This over-estimates FAB/LMB96 outcomes. (ii) Conversely, the reduced therapy arm of FAB/LMB96 demonstrated inferior outcome. Therefore, it would be inappropriate to compare the addition of rituximab to standard- *versus* reduced-intensity chemotherapy of FAB/LMB96. The actual 4-year EFS of all CNS^+ patients enrolled (not just randomized) on FAB/LMB96 was 70 ± 4.3%. Statistical analysis of FAB/LMB96, once corrected for the inferior arm of therapy, estimated the 4-year EFS at 75% ± 4–5% for CNS^+ patients (Table II), should all 111 patients have been treated on the C_1 arm (Cairo *et al,* 2007). More importantly, less than half of the events occurred in the CNS but were rather systemic relapses.

The 93.3% 4-year EFS of our pilot rituximab-containing chemoimmunotherapy study appears dramatically improved compared to 75% chemotherapy without rituximab. Importantly, if the addition of rituximab can significantly reduce systemic relapses, it could potentially enhance the EFS in CNS^+ patients, given that over 50% of the relapses in this population are systemic. The recently-closed European Intergroup/COG trial Inter-B-NHL 2010 trial (NCT01595048) randomized all high-risk patients (Group B stage III with elevated lactate dehydrogenase, Group B stage IV, Group C +/– CNS disease) to rituximab and was terminated early for strong beneficial signal in EFS in patients randomized to rituximab. Even this very large international study was unable to be powered to determine if rituximab was of clinical benefit in the relatively small subset of CNS^+ patients. Minard-Colin *et al,* 2016.

Rituximab represents a potential advance for this CNS^+ patient population. Intensifying up-front therapy in selected high-risk patients is a key future priority, because salvage rates in refractory/relapsed patients remain disappointing (Cairo *et al,* 2015, Jourdain *et al,* 2015).

Improving stratification and integrating targeted agents like rituximab are potential paths towards these goals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I.

Key risk factors in CNS^{+} patients on arm C_1 FAB/LMB96 and ANHL01P1

Treatment protocol	FAB/LMB96 C_1 arm (n=44)	ANHL01P1 Group C (n=15)	Total (n=59)	*P*-value
Marrow status				
BM^{-}	47.7% (21)	46.7% (7)	47.5% (28)	>0.99
BM^{+}, either M2 or M3	52.3% (23)	53.3% (8)	52.5% (31)	
<25% blasts	13.6% (6)	6.7% (1)	11.9% (7)	
≥25% blasts (Burkitt leukemia)	38.6% (17)	46.7% (7)	40.7% (24)	
CNS status				
CSF^{+}	54.5% (24)	53.3% (8)	54.2% (32)	>0.99
Isolated CSF^{+}	36.4% (16)	33.3% (5)	35.6% (21)	
CSF^{+} plus ≥1 of CNP, PME, ICM	18.2% (8)	20% (3)	18.6% (11)	
CSF^{+} and BM^{+}	36.4% (16)	33.3% (5)	35.6% (21)	
CSF^{-}	43.2% (19)	46.7% (7)	44.1% (26)	
Isolated CNP^{+}	13.6% (6)	13.3% (2)	13.6% (8)	
CNP^{+} plus ≥1 of PME, ICM	15.9% (7)	6.7% (1)	13.6% (8)	
Isolated PME^{+}	9.1% (4)	26.7% (4)	13.6% (8)	
PME and ICM	4.5% (2)	0	3.4% (2)	
Unknown	2.3% (1)	0	1.7% (1)	

BM, bone marrow; CNP, cranial nerve palsy; CNS, central nervous system; CSF, cerebrospinal fluid; ICM, intracerebral mass; PME, para-meningeal extension.

Table II.

EFS of all CNS^{+} patients on LMB89, FAB/LMB96 and ANHL01P1.

Clinical trial	Treatment regimen	4-year EFS
LMB89 (*n* = 67)	COP reduction, COPADM induction, and CYVE intensification chemotherapy plus 24 cGy CNS irradiation	79 ± 5.0%
FAB/LMB96, all patients (*n* = 111)	LMB89-based chemotherapy; CNS irradiation replaced by HD-MTX and additional IT chemotherapy, All CNS+ patients enrolled	*75 ± 4.5%
FAB/LMB96, C_1 patients (*n* = 44)	LMB89-based chemotherapy; CNS irradiation replaced by HD-MTX and additional IT chemotherapy, Standard arm patients	84.1% (95% CI: 70–92%)
ANHL01P1 (*n* = 15)	FAB/LMB96-based chemotherapy; no CNS irradiation; addition of rituximab, urate oxidase, and shorter doxorubicin infusion	93.3% (95% CI: 61–99%)

CI, confidence interval; CNS, central nervous system; COP, cyclophosphamide, Onconvin (vincristine), prednisone; COPADM, cyclophosphamide, Onconvin (vincristine), prednisone, Adriamycin (doxorubicin), methotrexate; CYVE, cytarabine and etoposide; EFS, event-free survival; HD-MTX, high-dose MTX; IT, intrathecal.

*Actual 4-year EFS on FAB/LMB96 of 70 ± 4 3% was statistically adjusted to account for patients with inferior outcomes randomized to reduced-intensity therapy (Cairo *et al,* 2007).