To the editor:

Stage IV adult sporadic Burkitt lymphoma/leukemia with complex bone marrow cytogenetics is associated with a very poor outcome

Adult Burkitt lymphoma/leukemia (BLL) is a rare, aggressive B-cell neoplasm with typical morphologic appearances. It is characterized by rapid proliferation of mature B cells (Ki67/MIB-1 staining ≥ 99%) and overexpression of *c*-Myc, which most commonly results from the translocation t(8;14) and less frequently from t(2;8) and t(8;22). Based on shared genetic and molecular features, the World Health Organization (WHO) classification now recognizes a lymphomatous and leukemic phase of this disease as a single entity.[1]

Overall improved outcomes with remission rates of 65% to 100% and long-term survival of 40% to 80% have been reported following introduction of intensive multidrug regimens such as CODOX-M/IVAC and Hyper-CVAD.[2-4] Furthermore, the addition of rituximab (RTX), a monoclonal anti-CD20 antibody, has further increased responses.[5] Recognized prognostic factors in BLL are old age, raised level of lactate dehydrogenase, poor performance status, and advanced stage disease and are used in some protocols to distinguish between low-risk and high-risk disease. Thus adjusting treatment intensity accordingly has proven beneficial.[2,4] Nevertheless, the majority of patients with advanced-stage disease achieve durable remissions if treated with these chemotherapy regimens. Recently, Mead et al reported the results of the MRC/NCRI LY10 trial.[6] They found a 2-year progression-free survival (PFS) of 64% (95% confidence interval, 51%-77%) following treatment with CODOX-M/IVAC in 58 patients with BLL and did not identify clinical differences relating to the disease sites involved at presentation.

In contrast, we have observed a very poor outcome of adult patients with sporadic BLL and bone marrow involvement. Between 1998 and 2008, 13 patients were diagnosed within the Greater Manchester area in the United Kingdom. All patients were HIV-negative and received treatment with alternating CODOX-M/IVAC as per LY06 or LY10, with or without RTX.[4,6] The median age was 42 years (range, 19-69 years). Patients were diagnosed by a specialist hematopathology service according to WHO criteria. Patient characteristics are summarized in Table 1. There were no treatment-related deaths. Four patients had refractory disease and subsequently died of disease progression; 4 patients underwent stem cell transplantation (SCT); patients 1 and 7 had an allogeneic sibling, patient 9 had a matched unrelated donor SCT, and patient 6 had an autologous SCT. All patients relapsed and died within 2 months of completing therapy. The median overall survival from diagnosis was 5 months (range, 4-17 months) and median progression-free survival was 3 months (range, 0-12 months). For those who achieved remission (n = 9), median time from completion of therapy to relapse was less than 1 month (range 0-12).

We believe that bone marrow involvement with complex cytogenetics is most important in determining prognosis in this

Table 1. Pretreatment patient characteristics

Patient	Sex	Age, y	Ann Arbor stage	WHO performance status	LDH	Primary site	Bone marrow cytogenetics
1	F	30	IV	1	1531	BM, neck mass	47,XX,der (1)del(1)(p31)add(1)(q42),der(1)del(1)(p12)add(1)(q42),der (2)add(2)(p15),+7,t(8;14)(q24;q32), t(8;14)(q24;q32),t(14;18) (q32;q21),add(17)(p13)
2	F	69	IV	2	NA	BM	45-47, X, add(X)(q2?6), del(1)(p13), add(4)(q35), −6, +7, t(8;14)(q24;q32), −10, add(10)(q2?4), del(13) (q12q14), t(14;18)(q32;q21), add(17)(p1?1), ?+21
3	F	24	IV	3	24 600	BM	49,XX,add(9)(p22),del(9)(p22), + mar x 3 [3]/ 46,XX [1]
4	M	50	IV	3	17 000	BM, axillary mass	51XY, der(1)t(1;1)(p36;q?21), +7, add(8)(p?), +12, add(14)(q32), +17, der(18)t(14;18)(q32;q21), +20,+21, der(22)t(8;22)(q24;q11)
5	M	19	IV	3	2137	BM, parotid mass, CNS	49,XY,+X,dic(1;1)(p11;q4?2),+7,+8,t(8;14)(q24;q32)[7]/50,XY,+X, +del(1)(p2?2),+7,+8,t(8;14)(q24;q32)[4]
6	M	60	IV	1	1326	BM	47, XY, t(2;8)(p12;q24), add(3)(q2?1), der(6)t(3;6)(q13;q1?3), der(8)t(3;8)(p21;p?21), −9, add(12)(p13), +?del(16)(q22), +18, add(20)(q1?1)
7	F	25	IV	3	6567	BM	45, X, -X, t(8;9;14)(q24;p13;q32)del(8)(p11)[12]/46, XX[2]
8	F	33	IV	3	2800	BM	46,XX,t(8;14)(q24;q32),der(13)t(1;13)(q11;q34)[10]/46,XX[1]
9	M	33	IV	2	20 000	BM	46,XY,t(2;8)(p12;q24), t(3;22)(q27;q11), t(14;18)(q32;q21) [1]/46,idem t(6;9)[4]/46,idem t(6;9), der(14), t(14;18)[2]/46,idem der(14), t(14;18)[2]/46,XY[1]
10	M	42	IV	2	27 150	BM	46, XY, dic dup(1)(p11q32), t(8;14)(q24;q32)[8]/92, indemx2[2]
11	M	66	IV	3	2309	BM	46, XY, dup1q(q23;q32), t(8;22)(q24;q32), del9q(q12;q22)
12	M	66	IV	2	1953	BM, CNS, abdominal mass	46XY, t(8:14)(q24:q32), del (13) (q14q22)[10]
13	M	59	IV	3	8133	BM	46XY, der (1) t(1:11)(q21;q13), t (2:18)(p12;q21), t(14;18)(q24;q32), −11, del(13)(q12q14), +mar[15]/46, idem, del(6)(q13q21)[3]/46,XY

BM indicates bone marrow; and NA, not available.

subgroup of BLL and would like to emphasize this observation. It would therefore be useful for the authors of the recently reported LY10 trial to perform a subgroup analysis for those patients with bone marrow involvement, and assess outcome with respect to their karyotypes. Furthermore, alternative treatment strategies are required for this subgroup of patients, as salvage treatments are rarely, if ever, successful in refractory or relapsed disease.[2,7,8] Further trials are needed to re-evaluate the role of SCT as well as other experimental treatments such as radioimmunotherapy (Zevelin) or molecular therapies targeting *c*-Myc.

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Response

Bone marrow involvement and outcome in Burkitt lymphoma and diffuse large B-cell lymphoma

Professor Yin and his colleagues at Manchester describe a series of 13 patients with aggressive B-cell lymphomas with bone marrow involvement who had a very poor outcome despite intensive treatment including allogeneic transplantation in 3 cases. In all of the tumors a *MYC* rearrangement was present, but in most cases this was in the context of a complex karyotype and in 4 of the patients a t(14;18) was also present.

The experience of the Manchester group serves to highlight the key point that emerged from the analysis of the MRC LY10 trial, which is that the effective targeting of intensive chemotherapy such as CODOX-M/IVAC in aggressive B-cell lymphomas requires a strict pathologic definition of Burkitt lymphoma.[1] In LY10 we proposed criteria based on germinal center phenotype, lacking BCL-2 expression, with a *MYC* rearrangement as the sole genetic abnormality. Although there are clearly gray areas, this approach is supported by published gene expression data and by other studies reporting the very poor clinical outcomes for B-cell lymphomas with complex cytogenetics, particularly where multiple balanced translocations are present.[2-4] When this definition is used, the data from LY10 shows that bone marrow involvement at presentation had only a small effect on outcome. 24/53 patients in the trial had marrow involvement and this group had a 2-year overall survival of 61.0% (95% confidence interval [CI] 41.0%-80.9%) compared with 72.1% (95% CI 55.7%-88.5%) for those with no marrow disease (Figure 1). Conversely, in the 16/56 DLBCL patients with marrow involvement, 2-year survival was only 16.7% (95% CI 0.1%-36.1%) compared with 75.0% (95% CI 61.6%-88.4%) in those with no marrow disease. It is possible that these results may