Leukemia (2005) 19, 945–952

www.nature.com/leu

Short intensive sequential therapy followed by autologous stem cell transplantation in adult Burkitt, Burkitt-like and lymphoblastic lymphoma

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The feasibility and efficacy of up-front high-dose sequential chemotherapy followed by autologous stem cell transplantation (ASCT) in previously untreated adults (median age 33 years; range 15–64) with Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL) or lymphoblastic lymphoma (LyLy), both without central nervous system or extensive bone marrow involvement was investigated in a multicenter phase II study. Treatment consisted of two sequential high-dose chemotherapy induction courses incorporating prednisone, cyclophosphamide, doxorubicin, etoposide and mitoxantrone, without high-dose methotrexate or high-dose cytarabine. Patients with at least PR went on with BEAM and ASCT. Protocol treatment was completed by 23/27 (85%) BL/BLL and 13/15 (87%) LyLy patients. Median treatment duration until BEAM was 70 (range: 50–116) days. No toxic deaths occurred. Response to treatment was complete response (CR) 81% and partial response (PR) 11% for BL/BLL, CR 73% and PR 20% for LyLy. At a median follow-up of 61 months of patients still alive, six BL/BLL and eight LyLy patients have died. The actuarial 5-year overall and event-free survival estimates are 81 and 73% for BL/BLL *vs* 46 and 40% for LyLy patients. In conclusion, this short up-front high-dose sequential chemotherapy regimen, followed by ASCT is highly effective in adults with BL/BLL with limited bone marrow involvement, but less so in patients with LyLy.
Leukemia (2005) **19,** 945–952. doi:10.1038/sj.leu.2403733
Published online 31 March 2005
Keywords: adult Burkitt lymphoma; autologous stem cell transplantation; lymphoblastic lymphoma; Burkitt-like lymphoma

Introduction

Sporadic Burkitt lymphoma (BL) is a rare and highly aggressive B-cell tumor.[1] Although it accounts for up to 40% of B-cell lymphoma in childhood, less than 5% of the lymphomas in adults are BL.

Age, central nervous system and/or bone marrow involvement, high serum LDH and bulky tumor mass at diagnosis are poor prognostic factors.[2–4] Current treatment strategies developed for children mainly consist of a relatively short course of intensive risk-adapted chemotherapy, incorporating (fractionated) cyclophosphamide, doxorubicin, vincristine and steroids in combination with high-dose intravenous methotrexate (MTX), high-dose cytarabine (Ara-C), and sometimes also etoposide.[3–7] With this type of approach, treatment outcome in children is excellent, with over 80% cure rates even in patients with adverse prognostic risk factors at diagnosis. As a result of the relative rareness of BL in adults, only few data on treatment outcome in these patients have been reported, with higher cure rates in adult patients treated with a 'pediatric' type of therapy approach.[8–12] However, children had superior outcome and tolerated treatment better than older patients.[8]

Lymphoblastic lymphoma (LyLy), a disease mainly seen in adolescents has a very poor outcome in adults treated with conventional chemotherapy. Adult patients with extensive bone marrow involvement at presentation have better outcomes with more intensive treatment approaches such as those used for treatment of acute lymphoblastic leukemia,[13–16] but the optimal treatment for patients with less extensive disease remains to be elucidated.

Based on promising results of autologous stem cell transplantation (ASCT) in patients with aggressive lymphoma in first remission, including nonleukemic BL, Burkitt-like lymphoma (BLL) and LyLy,[17–22] the Dutch–Belgian Hemato-Oncology Cooperative Group (HOVON) initiated a multicenter phase II study in December 1994 to evaluate a strategy of short intensive sequential chemotherapy, and subsequent ASCT in adult patients. We present the results of this treatment in patients with BL/BLL and LyLy with a median follow-up of more than 5 years for patients still alive.

Methods

Patients

Between December 1994 and February 2003, patients with newly diagnosed BL, BLL or LyLy in the Netherlands and Belgium were enrolled in a multicenter phase II study HOVON-27BL. Patients had to be fully staged, including CT scanning of the thorax and abdomen, bone marrow aspiration and biopsy, and cerebrospinal fluid examination. The following entry criteria had to be fulfilled: age 18–65 years, Ann Arbor stage II–IV, or I (E) in combination with either bulky (>10 cm) tumor

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From the Department of Hematology, University Medical Center Groningen, Groningen, The Netherlands. For The Dutch–Belgian Hemato-Oncology Cooperative Group (HOVON). Supported by the Dutch Cancer Foundation, Koningin Wilhelmina Fonds.
Received 14 December 2004; accepted 22 February 2005; Published online 31 March 2005

or with serum LDH > 1.5 times the upper normal limit of the participating institution; WHO-performance score 0, 1, or 2, no central nervous system (CNS) localization, and less than 30% bone marrow infiltration. Patients were not eligible if they were HIV-positive, or had severe concomitant disease, prior malignancy or major organ dysfunction not directly related to infiltration or obstruction by lymphoma. Except for treatment with steroids in the week before starting protocol treatment, no prior chemotherapy was allowed. Renal dysfunction due to tumor obstruction or hyperuricosemia was accepted at entry, but required correction before the start of treatment. In the present analysis, patients were retrospectively classified to the age-adjusted International Prognostic Index (aa-IPI), as well as a low- or high-risk group according to the risk grading based on Magrath *et al*[9] and used by the United Kingdom Lymphoma Group (UKLG) for BL[23] and others.[24] According to this grading system, patients with all of the following features present: (i) Ann Arbor stage I–II(E), (ii) tumor mass <10 cm, (iii) normal serum LDH, and (iv) WHO performance 0 or 1 were graded as low risk, all other patients as high risk. All patients gave informed consent for study participation according to the regulations of the Dutch health authorities. The study was performed and evaluated by HOVON according to the Helsinki agreement.

Pathology

Biopsies were reviewed and classified both according to the REAL[25] and WHO[1] classification schemes. Tissue blocks were collected to perform additional fluorescent *in situ* hybridization (FISH) analysis for the detection of MYC/8q24 breakpoints.[26]

Treatment

Initial treatment consisted of two consecutive high-dose chemotherapy combinations. Induction-I consisted of 1000 mg/m^2 cyclophosphamide i.v., 12 hourly on days 1 and 2 (total dose: 4000 mg/m^2); 35 mg/m^2 doxorubicin i.v., on days 1 and 2 (total dose 70 mg/m^2); 100 mg prednisone for 5 days. Uromithexan (Mesna) 200 mg/m^2 was infused every 4 h, starting 10 min before the cyclophosphamide infusion; the final uromithexan infusion was administered 8 h after the last cyclophosphamide infusion. Induction-II consisted of 250 mg/m^2 etoposide, every 12 h i.v. for 4 days (total dose 2000 mg/m^2); 30 mg/m^2 mitoxantrone i.v. on day 1; and 100 mg prednisone for 5 days. Induction-II was given as soon as hematological recovery, defined as a rising platelet and neutrophil count in excess of 100×10^9/l and 1.0×10^9/l, respectively, was observed after induction-I. After each induction course, patients received 5 μg/kg G-CSF (Filgrastim) s.c. daily from day 5 until a neutrophil count (ANC) was observed of at least 0.5×10^9/l for two consecutive days.

Peripheral blood stem cells were harvested and cryopreserved preferably after induction-I or otherwise after induction-II according to standard institutional harvesting procedures, provided the bone marrow did not contain lymphoma on histology (anymore). No CD34 selection or purging was performed. Patients attaining at least a partial response (PR) after induction-II, and from whom a sufficient stem cell harvest of at least 2.5×10^6 CD34$^+$ cells/kg had been obtained, were subsequently treated with high-dose therapy and ASCT. High-dose chemotherapy consisted of BEAM: 300 mg/m^2 carmustine i.v. on day -6; 100 mg/m^2 etoposide, infused in 1 h, every 12 h, for a total of 4 days starting on day -5; 100 mg/m^2 Ara-C, infused in 1 h, every 12 h, for 4 days starting on day -5; 140 mg/m^2 melphalan i.v. on day -1. Stem cells were reinfused on day 0. Intrathecal MTX 15 mg was used as CNS prophylaxis and administered at diagnosis, during induction-I, after recovery from induction-I and -II, and before BEAM for a total of five injections.

During treatment, all patients received hematological supportive care according to the rules and guidelines of the participating institution. This included vigorous hydration, allopurinol, platelet- and red blood cell transfusions, prophylactic oral antibacterial and antifungal treatment, as well as immediate treatment with i.v. broad-spectrum antibiotics and/or i.v. antifungal treatment in case of fever and/or documented or suspected infection. Patients with bulky disease at presentation ($\geqslant$10 cm) could be treated with additional (involved field) radiotherapy on PR sites after recovery from ASCT. This was left to the discretion of the treatment center. No further maintenance therapy was given.

Response to treatment and toxicity

Tumor response was assessed after induction-II, after ASCT, and after additional radiotherapy (if given) according to staging procedures described at diagnosis. Responses were classified as complete response (CR), unconfirmed complete response, PR, stable disease or progressive disease.[27] All side effects except hematological toxicity, nausea and hair loss were graded according to the National Cancer Institute Common Toxicity Criteria grading system. Infectious events were graded according to the WHO grading system for infections. Hematological recovery after each treatment course was assessed separately.

Statistical analysis

The data were analyzed as of July 2004. The study end points were CR rate, response rate (CR + PR), event-free survival (EFS), progression-free survival (PFS) and overall survival (OS). All survival end points were calculated from start of treatment on an intention-to-treat basis. EFS was defined as the time to progression, relapse or death from any cause, whichever came first. Patients without progression or relapse, who were still alive, were censored at the date of last contact. PFS was calculated from start of induction-I until progression, relapse or death from NHL; patients without progression or relapse who were still alive at the date of last contact, or who died from a non-NHL-related cause, were censored. OS was defined as the time to death from any cause; patients still alive were censored at the date of last contact.[27] However, as none of the patients died from a non-lymphoma-related cause, EFS and PFS were equal, and therefore PFS will not be considered separately. The Kaplan–Meier method was used to estimate OS and EFS and 95% confidence intervals (CI) were calculated. Kaplan–Meier survival curves were generated to illustrate survival, and the log-rank test was used to compare survival between subgroups. All reported *P*-values are two-sided and a significance level of $\alpha = 0.05$ was used.

Results

From 12 centers 42 patients with an original diagnosis of BL or BLL ($n=27$), T-lymphoblastic lymphoma (T-LyLy) ($n=13$) or B-lymphoblastic lymphoma (B-LyLy) ($n=2$) were included in the study. All lymphoblastic cases were confirmed upon

pathology review that included staining for terminal deoxynucleotidyl transferase (TdT). At review, particular attention was paid to the well-known difficulties in differentiating between BL, BLL and diffuse large B-cell lymphoma (DLBCL) according to the REAL classification[25,28] as well as BL, atypical BL (aBL) and DLBCL according to the WHO classification.[1] Review included histology, immunophenotype (B-cell markers, Ki-67/MIB1, CD10 and bcl2) as well as FISH for breakpoints in MYC/8q24.[26] A total of 27 cases with a diagnosis of BL or BLL as defined by the REAL classification had been included. All cases showed a classical starry sky pattern and a monotonous proliferation of medium-sized blasts as well as many mitotic figures with a Ki-67/MIB-1 proliferation index of $>90\%$. Morphological details varied to some extent, some cases having slightly more variation in nuclear size and the number of nucleoli (BLL). Moreover, all cases were of mature B cell origin (CD20 positive and immunoglobulin positive and/or TdT negative). Thus, also upon review, all cases fulfilled the criteria of the REAL classification for BL or BLL. However, in view of the current uncertainty on the histogenesis of BLL, all cases were also reviewed according to the WHO classification, which requires the presence of a MYC/8q24 breakpoint in all cases with atypical morphology to ascertain a diagnosis of aBL; in consequence, all aBL cases lacking this breakpoint should be classified as DLBCL. In 17 of 27 tumors, FISH for MYC/8q24 breakpoint detection was successfully performed. Of these 17 cases, 10 contained a MYC/8q24 breakpoint and seven were negative, the latter cases all being reviewed as DLBCL according to the WHO classification. For four cases with a classical histology and phenotype of BL in which no FISH analysis could be performed, a diagnosis of BL was maintained. Six cases with a morphology of aBL and/or phenotype, without material necessary for FISH, were reviewed as not evaluable.

Patient characteristics

The main clinical characteristics of both the BL and LyLy patients are summarized in Table 1. The median age was 33 years, two patients with BL/BLL were older than 60 years. Most patients presented with a good performance status. All stage I(E) patients had both elevated serum LDH as well as bulky disease. Stage IV disease and bone marrow involvement was observed more frequently in patients with LyLy. Half of the patients with BL/BLL and two-thirds of the patients with LyLy presented with extranodal involvement. As expected, the gastrointestinal tract was the most frequent site of extranodal involvement in patients with BL/BLL ($n=7$), but a variety of other sites of involvement were observed as well (lung, pericardial pleural in four, urogenital in three, bone marrow in two, and liver, ascites, epidural, breast, paranasal sinus, adrenal and soft tissue in one patient each). No apparent difference in clinical presentation was detected between the different morphological subgroups and between the breakpoint positive, negative, and not tested cases of BL/BLL. All patients with LyLy except one had a mediastinal mass at presentation. Lung, pericardial, or pleural involvement was observed in 44%. According to the aa-IPI, 37% of the BL/BLL and 53% of the LyLy patients had high-intermediate or high risk. Serum LDH levels were elevated in two-thirds of the patients, and in the majority of those patients in excess of 1.5 times the upper normal level. All but three patients had high-risk lymphoma according to the UKLG risk score.

Table 1 Patient characteristics

	BL/BLL		*LyLy*	
	n	*(%)*	n	*(%)*
Patients	27	*(100)*	15	*(100)*
Age median (years)	36		30	
Range	(15–64)		(16–50)	
Sex				
Male	21	*(78)*	13	*(87)*
Female	6	*(22)*	2	*(13)*
Stage				
I(E)	5	*(19)*	2	*(13)*
II	10	*(37)*	1	*(7)*
III	2	*(7)*	3	*(20)*
IV	10	*(37)*	9	*(60)*
B symptoms	13	*(48)*	6	*(40)*
Bulky (>10 cm) tumor	12	*(44)*	9	*(60)*
Bone marrow involved	2	*(7)*	3	*(20)*
Extranodal involvement	13	*(48)*	10	*(67)*
$\geqslant 2$ Extranodal sites	7	*(26)*	4	*(27)*
WHO performance score				
0–1	23	*(85)*	14	*(93)*
>1	4	*(15)*	1	*(7)*
LDH				
$\leqslant$ULN	9	*(33)*	5	*(33)*
1–1.5 $\times$ ULN	7	*(26)*	4	*(27)*
$>1.5\times$ ULN	11	*(41)*	6	*(40)*
Age-adjusted IPI				
0–1	17	*(63)*	7	*(47)*
2–3	10	*(37)*	8	*(53)*
UKLG-index				
Low risk	3	*(11)*	0	*(0)*
High risk	24	*(89)*	15	*(100)*

BL/BLL: Burkitt, Burkitt-like lymphoma; LyLy: lymphoblastic lymphoma; ULN: upper limit of normal; IPI: International prognostic index; UKLG- index: United Kingdom Lymphoma Group risk index for Burkitt lymphoma.[23]

Treatment course

Treatment according to the protocol including ASCT was completed by 23 (85%) BL/BLL and 13 (87%) LyLy patients. No patient failed to mobilize adequate numbers of CD34-positive cells for transplantation. Involved field radiotherapy after ASCT was given to six BL/BLL and four LyLy patients. Induction-II was given at a median of 27 days (range 16–51) and BEAM followed by ASCT at a median of 70 days (range 50–116) after the start of treatment. Six patients (four BL/BLL and two LyLy) did not complete treatment because of progressive disease ($n=3$), less than partial response ($n=1$), persistent bone marrow involvement after induction-II ($n=1$), or pulmonary embolism ($n=1$). Three of these patients ultimately reached CR off protocol.

Toxicity

No toxic deaths occurred. The median time from start of treatment to WBC recovery $>1.0\times10^9$/l was 14 days (range

Table 2 Toxic side effects by treatment course

Toxicity CTC-grade	*Percentage of patients with toxicity*							
	Induction-I (n = *42*)		*Induction-II* (n = *41*)			*ASCT* (n = *36*)		
	2	*3*	*2*	*3*	*4*	*2*	*3*	*4*
Oral	12	2	32	12	27	17	17	17
Cutaneous/allergy	7	—	5	—	—	8	—	—
Liver	5	5	—	2	—	8	—	—
Hemorrhage	2	—	—	—	—	3	—	—
Diarrhea	—	2	7	—	—	8	3	—
Renal	—	2	—	—	—	—	—	—
Cardial	2	—	2	—	—	6	—	—
Neurotoxicity	5	2	5	—	—	8	3	—
Bone pain	2	—	—	—	—	—	—	—
Other	29	2	20	5	—	22	6	—
Infections (WHO grade)	31	10	46	10	—	25	25	—

0–17) after induction-I, 15 days (range 5–29) after induction-II and 13 days (range 8–30) after ASCT. The median time from start of treatment to platelet recovery $>20 \times 10^9$/l was 13 days (range 0–26) after induction-I, 15 days (range 0–25) after induction-II and 10 days (range 0–99) after ASCT. WHO grade 2–3 infections were seen in 40% of patients during the aplastic phase after induction-I, in 56% after induction-II and in 50% after ASCT. No patient had WHO grade 4 infection. Severe mucositis, with CTC grade 3–4 was observed in 39% of the patients after induction-II, and in 39% after BEAM. This was the major nonhematological toxicity (Table 2). No other grade 4 toxicity was observed.

Response and survival

Response to treatment is summarized in Table 3. The overall response on protocol was 93% for both BL/BLL and LyLy. Disease progression (including relapse) was observed during treatment in one (4%) BL/BLL and two (14%) LyLy patients, and after completion of treatment in seven (26%) BL/BLL and seven (47%) LyLy patients. The primary site of progression was nodal (three BL/BLL, three LyLy), extranodal (four BL/BLL, two LyLy), or both (one BL/BLL, two LyLy). Specifically, meningeal disease was observed thrice, in one BL/BLL patient and one LyLy patient during induction-II, and after ASCT in one BL/BLL patient. No relapses were observed in the six BL patients who underwent radiotherapy. Two of the four patients with LyLy who underwent local radiotherapy progressed after 6 and 20 months, both inside (mediastinal) as well as outside the irradiation field. Three patients with progression (two BL/BLL and one LyLy) are still alive. With a median follow-up of 61 months of patients still alive, 14 patients have died, all of lymphoma. No other fatal events were observed. OS at 5 years is estimated to be 81% for BL/BLL (95% CI 61–92) and 46% for LyLy (95% CI 20–68). EFS at 5 years is 73% for BL/BLL (95% CI 51–86) and 40% for LyLy (95% CI 16–63). Kaplan–Meier curves of OS and EFS are depicted in Figure 1. No apparent differences were noted in the probability of reaching a complete remission or progression of disease for age, performance status, stage, number of extranodal sites, LDH, aa-IPI, UKLG risk, the different morphological subgroups or between the breakpoint positive, negative, and not tested cases in BL/BLL. These subgroups were obviously too small to draw any firm conclusion. Notably, despite the similar initial response rate of patients with BL/BLL and LyLy, patients with BL/BLL were far less likely to progress than patients with LyLy.

Table 3 Response and events

	BL/BLL		*LyLy*	
	n	*(%)*	n	*(%)*
Patients	27	*(100)*	15	*(100)*
Response on protocol				
Complete remission	22	*(81)*	11	*(73)*
Partial remission	3	*(11)*	3	*(20)*
Progression of disease	8	*(30)*	9	*(60)*
Progression before ASCT	1	*(4)*	2	*(14)*
Progression after ASCT[a]	7	*(26)*	7	*(46)*

BL/BLL: Burkitt, Burkitt-like lymphoma; LyLy: lymphoblastic lymphoma.
[a]Median follow-up 61 months.

Discussion

With a median follow-up of more than 5 years, this short intensive therapy followed by BEAM and ASCT could cure 80% of patients with BL/BLL without CNS or extensive bone marrow involvement. However, results in patients with LyLy were less favorable. Treatment of adult patients with ASCT according to this protocol was feasible in a multicenter setting. Although mucosal toxicity was extensive, no patient died of toxicity and serious other toxicities were not observed. Treatment duration was short, with a median time to last chemotherapy treatment of only 2.3 months. As has been shown by others (Table 4), a short duration of intensive therapy can be highly effective in BL/BLL. The initial CR rate is high in most series with only few patients progressing after 2 years.

When our results of up-front ASCT in adult BL/BLL are compared to those of other treatment approaches reported in the literature, several confounding issues must be addressed, in addition to the fact that reports of treatment results on adults are sparse. In general, the pathological diagnosis of BL in adult patients is extremely difficult.[28] Diagnostic difficulties mainly concern some cases of DLBCL with BL features or BL with somewhat variation in nuclear size and nucleolar distribution, often called BLL in the REAL classification[25] or aBL in the WHO classification, the latter defined as a variant of BL with a proven *MYC*/8q24 breakpoint.[1] In previous clinical studies concerning treatment outcome of BL, these variants have often been lumped together, especially since ancillary techniques like FISH were

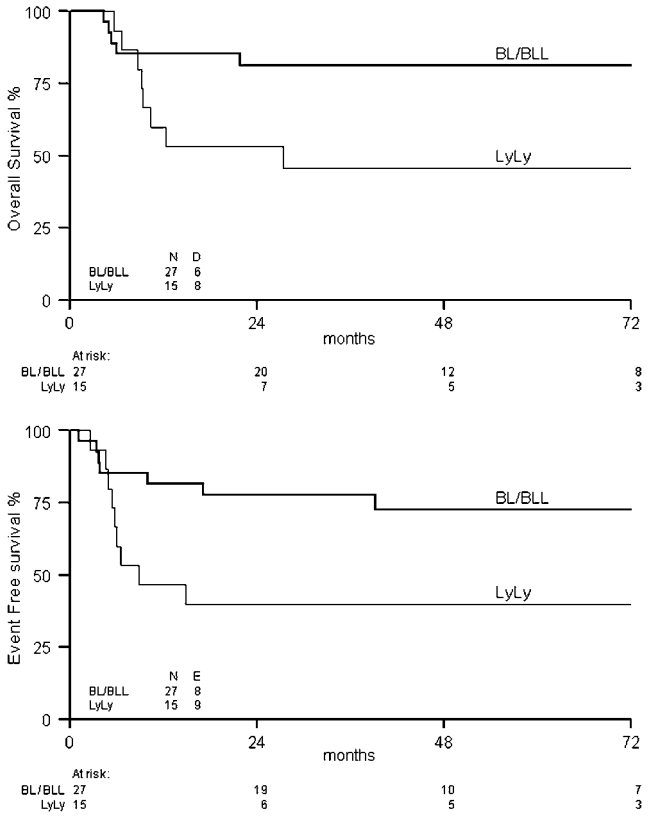

Figure 1 Overall survival and event free survival of BL/BLL and LyLy patients.

not available. In addition, it has been argued that as BLL represents a high-grade aggressive lymphoma much closer to BL than DLBCL, inclusion of BLL as a variant of BL is biologically and clinically more appropriate than absorbing the category of BLL into DLBCL.[29] Thus, until now, tumor morphology and immuno-phenotype have been used as main diagnostic criteria for patient entry in prospective clinical studies on BL and we are not aware of clinical studies prospectively based on inclusion of only *MYC*/8q24 positive cases. Although considered to be the pathogno-monic hallmark of BL, *MYC*/8q24 breakpoints are not exclusively found in BL but can also be detected in some morphologically undisputed cases of DLBCL.[30] Further-more, not all BL have a breakpoint that can be detected by currently used FISH assay.[26] Moreover, whether the presence of a *MYC*/8q24 breakpoint in itself confers a specific prognostic value for outcome of treatment still remains to be investigated. In the present series of 27 BL/BLL, according to the REAL classification, no apparent difference in clinical presentation or outcome was detected between the different morphological subgroups and between the breakpoint positive, negative, and not tested cases; however, numbers of patients obviously were too small to draw any firm conclusions.

Although prognostic factors have been recognized in BL, no formally validated risk classification according to prognostic factors exists for BL, making comparison of treatment outcome of different studies difficult. For instance, according to the IPI[7] only 37% of our BL/BLL patients had high-risk disease, but this index has been primarily designed for and validated in patients with aggressive lymphoma treated with CHOP-like chemotherapy excluding BL/BLL and LyLy. In childhood BL, the St Jude staging system as developed by Murphy[31] has been widely used for risk classification. According to this classification, 17 (62%) of our BL/BLL patients had advanced stage disease. For reasons of comparison with other recently published treatment regimens of adult patients with BL/BLL, we have also reclassified our patients according to the UKLG risk score.[23] This score, which is equivalent to that used by investigators at NCI in trials 77-04 and 89-C-41 for both childhood and adult BL[9] and in Boston for adult BL/BLL,[24] showed that 89% of our patients could be classified as high-risk BL/BLL.

Treatment with DLBCL-like regimens may be curative in patients with low-risk BL, presenting with nonextensive, nodal disease.[32–36] However, this treatment approach is not sufficient in patients with high-risk disease, that is, more extensive and extranodal disease, especially in the presence of extensive bone marrow and/or CNS involvement.[9] Remarkable improvements in the outcome of patients with high-risk disease, even in those with overt leukemic BL or CNS involvement, have been attributed to the addition of high-dose intravenous MTX and Ara-C to the treatment in children[3,4,6] as well as in adults.[8–12,23,24,37] At high dosages both drugs penetrate well the CNS, which may be one of the reasons of their apparent efficacy. The HOVON-27BL does not contain high-dose MTX and only low-dose Ara-C in the BEAM regimen. Although CNS prophylaxis was mandatory in patients with BL and LyLy at the time this study started, the optimal prophylaxis including the type and amount of (intrathecal) drugs was still under debate and the toxicity of high-dose intravenous MTX and or Ara-C, especially in elderly patients, well documented.[8–12] Apart from intrathecal MTX (at that time our standard prophylactic intrathecal regimen for lymphoma), our protocol incorporated intravenous high-dose etoposide in the induction regimen as well as high-dose carmustine in the BEAM regimen, drugs both well able to penetrate the blood–brain barrier. We omitted high-dose intravenous MTX or Ara-C in our regimen to avoid possible excessive toxicity. Whether, in retrospect, this was sufficient for CNS prophylaxis in BL patients without extensive CNS or bone marrow involvement is debatable, given one BL with meningeal disease during induction treatment.

In contrast to our results in BL/BLL, patients with LyLy fared less well. The discrepancy between LyLy and BL treated with the same regimen is remarkable, suggesting that treatment outcome is more dependent on the type of tumor cell than on clinical presentation. BL, like most aggressive lymphomas originating from follicle center cells, seems to respond well to this lymphoma-type regimen. In contrast, LyLy, derived from precursor B- or T-cells, ultimately responded poorly to this short treatment. Although a comparable complete remission rate of 73% was reached, a substantial number of patients with LyLy relapsed and EFS was only 40% at 5 years. The number of LyLy patients treated with this regimen was too small to draw firm conclusions on any relation with either original extent of disease or the pattern of relapse. As has been the experience in the treatment of children with LyLy,[38] this type of lymphoid malignancy probably needs treatment of longer duration as in acute lymphoblastic leukemia.[39] We and others have reported excellent results with 2–3 years maintenance therapy together with consolidation courses after induction chemotherapy in adult precursor B- and T-ALL.[16,40] Whether additional benefit can be obtained by ASCT in patients in first CR remains questionable. A randomized multicenter study in adult patients with LyLy, comparing ASCT with conventional-dose chemotherapy in patients responding to induction chemotherapy failed to show a survival benefit for the ASCT arm, although this study had to be closed before the projected number of patients was reached because of accrual problems.[41]

Table 4 Overview of adult Burkitt, Burkitt-like/small non-cleaved-cell lymphoma treatment

Reference	*Histology*	*Patients number*	*Age median (range)*	*Ann Arbor stage III–IV*	*BM+*	*CNS+*	*Regimen*	*MTX (g/m^2)*	*Etoposide (mg/m^2)*	*Ara-C (mg/m^2)*	*Last Treatment months after diagnosis*	*Complete response*	*Median follow-up months (range)*	*Actuarial overall survival*
SNCCL								Per cycle	Per cycle	Per cycle				
Bernstein 1986	SNCCL	18	25 (15–75)	44%	11%	0%	M-CHOP/XRT	3	none	none	4–6	78%	14	67% 2y
Lopez 1990	SNCCL	45	32 (17–72)	59%	16%	2%	MDA 81-01/84-30	1	100 × 3	200 × 8	6.4	80%	nk	52% 5y
McMaster 1991	SNCCL	20	45 (21–69)	90%	30%	15%	M-BCHEOP	0.2	100–400 × 3	none	2	85%	29	60% 5y
Longo 1994	SNCCL	33	36 (19–80)	49%	9%	0%	ProMACE+	3–0.1	100	300	8	82%	120	60% 10y
Magrath 1996	SNCCL	39	24 (18–56)	77%	nk[a]	nk	NCI 77-04	2.8	none	none	15	nk	(72–200)	56% 5y
BL														
Magrath 1996	BL	20	25 (18–59)	70%	nk[b]	nk[b]	NCI 89-c-41	6.7	60 × 5	2000 × 4	3.8	100%	32	100% 3y
Mead 2002	BL	52	35 (15–60)	61%	40%	13%	UKLG LY06	6.7	60 × 5	2000 × 4	2.3	77%	35	73% 2y
Lacasce 2004	BL	14	47 (18–65)	nk	36%	0%	Modified Magrath	3	60 × 5	2000 × 4	nk	86%	29	71% 2y
Di Nicola 2004[d]	BL	22	36 (18–76)	50%	14%	5%	INT, Milan	[e]	250 × 2	1750 × 4	3	77%	29	77% 12y
Current Study	**BL**	**27**	**36 (15–64)**	**44%**	**7%**	**0%**	**HOVON-27BL**	**none**	**250 × 8**	**none**	**2.3**	**81%**	**61**	**81% 5y**
BL & Leukemic														
Soussain 1995	BL	65	26 (17–65)	70%	33%[f]	18%	LMB 84,86,89	3–8	200 × 4	3000 × 3	2.5	89%	57	74% 3y
Lee 2001	BL	54	44 (18–71)	nk	61%	4%	NHLB86	1.5	80 × 2	150	5.1	80%	61	52% 5y
BL Leukemic														
Hoelzer 1996	BL	24	36 (18–65)	Leukemic	100%	12%	NHL-B83	0.5	165	300 × 4	5.3	63%	nk	49% 8y
Hoelzer 1996	BL	35	33 (18–58)	Leukemic	100%	12%	NHL-B86	1.5	100 × 2[c]	150 × 4		74%	nk	51% 4y
Thomas 1999	BL	26	58 (17–79)	Leukemic	100%	42%	Hyper-CVAD	1	none	3000 × 4	5.3	81%	nk	49% 3y

BL: Burkitt and Burkitt-like lymphoma; SNCCL: small non-cleaved-cell lymphoma.
[a]nk: not known (not reported).
[b]not known: 3 patients with either BM or CNS involvement.
[c]VM26.
[d]Patients not in CR or relapse were treated with rituximab with high-dose therapy and autologous stem cell transplantation.
[e]150 mg/kg d 7 and 250 mg/kg d 21.
[f]number of patients with >50% blasts in bone marrow.

Given the small numbers of adult patients with BL/BLL, the different mix of risk factors, histologies, staging classification and follow-up presented in the literature, it is difficult to directly compare the results of the HOVON-27BL regimen with those of other treatment schemes (Table 4). The 81% OS and 73% EFS, at 5 years are excellent, without the use of high-dose MTX and high-dose Ara-C. Evidently, only phase III trials can answer the question how this scheme compares to the usually applied regimens for adult patients with BL/BLL. Given the rarity of the disease in adults, this will require a world wide intergroup organization.

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