Treatment of Burkitt’s/Burkitt-like lymphoma in adolescents and adults: a 20-year experience from the Norwegian Radium Hospital with the use of three successive regimens

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Background: Burkitt’s/Burkitt-like lymphoma (BL/BLL) are highly aggressive lymphomas mainly affecting children and young adults. We report the results in adolescent and adult patients with the use of three successive regimens.

Patients and methods: Forty-nine patients aged 15–70 years admitted to the Norwegian Radium Hospital in the period 1982–2001 with a diagnosis of BL/BLL on histological review and who were given chemotherapy with curative intent are included in this analysis. Up to 1987 patients were given doxorubicin-based chemotherapy supplemented with intravenous and intrathecal methotrexate (MmCHOP). From 1987 to 1994, patients who obtained complete remission upon this regimen were consolidated with high-dose therapy with stem-cell support (MmCHOP + HDT). In 1995 we introduced as frontline therapy the German Berlin–Frankfurt–Munster (BFM) regimen.

Results: By intention to treat analyses, the progression-free survival rates for patients who received MmCHOP ($n=13$), MmCHOP + HDT ($n=17$) or BFM therapy ($n=19$) are 30.8%, 70.6% and 73.7%, respectively. In the groups of patients who received either the BFM regimen or MmCHOP + HDT, all patients who obtained complete remission upon induction therapy are continuously disease free. There was no treatment-related death.

Conclusions: BL/BLL in adolescents and adults can successfully be treated with 5-day blocks of intensified chemotherapy such as the BFM regimen or CHOP/methotrexate-based chemotherapy consolidated with high-dose therapy. Using the BFM regimen, continuous remissions are obtained without additional myeloablative chemotherapy.

Key words: BFM chemotherapy, Burkitt’s lymphoma, high-dose therapy

Introduction

Burkitt’s/Burkitt-like lymphoma (BL/BLL) are highly aggressive B-cell lymphomas that most commonly affect children, adolescents and young adults. Left untreated, the disease is rapidly fatal [1].

Standard doxorubicin-based combination chemotherapy, such as CHOP, frequently induces remissions of short duration [2, 3]. In an attempt to obtain durable remissions, high-dose therapy (HDT) with autologous stem-cell support was given in a few centres for patients who were in remission upon CHOP-like induction therapy [4–6]. In the last decade, several paediatric groups have obtained impressive results for BL- and B-cell acute lymphoblastic leukaemia patients by giving blocks of intensified chemotherapy for five to seven consecutive days with 2- to 3-week intervals [7–11]. In the German Berlin–Frankfurt–Munster (BFM) regimen, fractionated cyclophosphamide and ifosfamide as well as high-dose methotrexate with calcium folinate rescue and central nervous system (CNS) prophylaxis appear to be of special importance [10–12]. The treatment is of brief duration, and it does not contain maintenance therapy. The intensity and duration of the chemotherapy is modified by the risk category of the lymphoma. Five-year disease-free and overall survival >90% in paediatric patients have been reported from this and other groups. In the German Adult Acute Lymphoblastic Leukaemia (ALL) 05/93 protocol, the BFM-90 protocol was adjusted with dose modifications for adult patients.

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The Norwegian Radium Hospital (NRH) is the referral centre for diagnosis and treatment of lymphoblastic and Burkitt’s lymphoma in South/East Norway, serving a population of ~2 million inhabitants. During the time period 1982–2001, 49 patients were admitted with a diagnosis of BL/BLL and given therapy with a curative intent. All these patients are included in the current analysis. Between 1982 and 1987, 13 patients aged 15–60 years received standard doxorubicin-based therapy supplemented with intravenous and intrathecal methotrexate (MmCHOP). In the following period (1987–1994) patients in the same age group (n = 17) with chemo-responsive disease on induction with MmCHOP, were given consolidating HDT with autologous stem-cell support. From 1995, 19 patients aged 15–70 years have been treated according to the BFM protocol. Here, we report on the outcome of patients treated with the various regimens.

Patients and methods

Patients

All patients treated for lymphoma at NRH have been registered prospectively in our lymphoma database, established in 1981. The database, now including more than 5000 patients, contains information on histology, symptoms, staging, results of blood tests, clinical findings at diagnosis, treatment and follow-up. Patients who were referred for the first time to NRH in the period 1981–2001 and were diagnosed with BL/BLL with an age >15 years and <60 years (70 years from 1995) were eligible for this retrospective analysis. One patient was lost to follow-up in our database, and survival has been retrieved from the National Population Registry. Staging included clinical examination, chest X-ray, computed tomographic scan of the abdomen and the thorax (CT of the thorax from 1990), ultrasound of the liver and spleen, standard blood tests and bone marrow aspiration and biopsy. Cerebrospinal fluid was routinely examined for malignant cells. Clinical stage was classified according to the Ann Arbour system [13].

Diagnosis and pathology review

All histological material from the cases included has been reviewed for the study, and the diagnoses were established according to the World Health Organisation (WHO) criteria [14].

Immunomagnetic purging and haemopoietic progenitor cell assessment

Mononuclear cell (MNC) fractions were prepared either by the use of a 2991 Cobe Cell Processor (1185, Oak Street, Lakewood, USA) and Ficoll (Lymphoprep, Nycomed, Oslo, Norway) or without Ficoll in a CS-3000 Plus Blood Cell Separator (Baxter Blood Cell Corporation, Fenwal Division, Deerfield, IL, USA). One patient received stem cells harvested from blood (PBPC). The combination of antibodies used for purging with immunomagnetic beads was selected on the basis of the antigen expression of the individual B-cell lymphomas. Anti-CD19, CD20, CD22, CD23, CD37 monoclonal antibodies of IgG subtypes were used (Baxter Biotech, Deutschland GmbH, Immunotherapy Division, Munich, Germany). The purging efficacy and safety using immunomagnetic beads are described elsewhere [15, 16]. All patients except two received a purged graft.

Treatment

From 1982 to 1987 patients up to age 60 years received eight courses of CHOP supplemented for the first six cycles with an intermediate dose of methotrexate (2g/m²) given intravenously with calcium folinate rescue and intrathecal (12 mg) methotrexate (MmCHOP). From 1987 to 1994, patients who obtained a complete or very good partial remission upon MmCHOP were, after oral and written informed consent, included in a phase II study. In this study, approved by the Local Ethics Committee, the patients received additional high-dose therapy [cyclophosphamide 120mg/kg and total body irradiation (TBI), 13 Gy in 10 fractions/5 days, dose to the lungs reduced to 10.4 Gy]. The harvested and purged bone marrow cells (11 of 13 patients) or purged PBPC (one patient) were subsequently thawed and reinfused through a central line. From 1995, patients received therapy according to BFM protocol-90 ([11] and Figure 1) with methotrexate adjustments for patients >50 years as described in the German Adult ALL 05/93 protocol. In addition, patients were stratified into therapy arms by risk groups according to the protocol [12]. Patients who only obtained a partial remission after BFM therapy were candidates for HDT with the BEAM regimen. According to the ASCO guidelines [17], patients who were treated with the BFM regimen after 1997 received growth factor support with filgrastim injections to alleviate neutropenia.

End points and statistics

Treatment success was determined by the rate of overall and progression-free survival (PFS). Overall survival was measured from diagnosis to death of any cause, PFS from diagnosis to the first observation of disease progression or death from B/BL lymphoma. Chi square or Fisher tests were used to compare differences between treatment groups. For survival analysis, the Kaplan–Meier method was used.

Results

Patient characteristics

Forty-nine patients are included in this retrospective analysis: 13 in the period 1982–1987, 17 from 1988 to 1994 and 19 from 1995 to 2001. The median ages in the three groups were 30, 31 and 36 years, respectively, and the median follow-up times of survivors were 190, 127 and 48 months. Table 1 lists the distribution of age, stage, bulky disease ≥10 cm in the greatest transverse diameter and International Prognostic Index (IPI) score in the three treatment groups. There is no significant difference amongst the three groups regarding any tumour or patient-related factors.

High-dose therapy

Fourteen patients received HDT; 12 following complete remission (CR) upon MmCHOP therapy and two patients after BFM therapy. For the BFM patients, one patient was consoli-
dated with HDT (cyclophosphamide 120 mg/kg and TBI) despite CR upon two BFM courses. The second patient received HDT (BEAM) according to protocol due to partial remission after BFM-based therapy.

Toxicity and engraftment after high-dose therapy

Bone marrow engraftment occurred in all patients, except for one patient who had previously received BFM therapy and transplanted in partial remission. He never reached absolute neutrophil count (ANC) >0.5 × 10⁹/l and progressed 1 month after transplantation. There were no treatment-related deaths. The median time for ANC recovery (>0.5 × 10⁹/l) was 19 days.
range 9–27), and the median time for platelet recovery 
(range >20 × 10^9/l) was 21 days (range 12–196). Use of filgrastim 
after HDT has not been standard treatment at our 
institution. Thus, only three patients received filgrastim after 
HDT. One patient with delayed platelet engraftment had 
haemorrhagic cystitis with no major complications and she 
also had an epidural bleeding 3 months after HDT, from 
which she recovered without sequelae.

**Toxicity and feasibility of BFM therapy**

Nineteen patients received one to seven courses with BFM 
thrapy. Thirteen patients received the planned therapy without 
dose reduction. Two patients received only one course due 
to early death, and four had minor dose reductions (5–10%) due 
to mucositis. For the 17 patients that received more than one 
course, five had no delay in therapy, nine had up to 1 week 
total delay and three 1–2 weeks delay. Delayed haematological 
reconstitution was the main cause of prolonged treatment dur-
tion. Therapy was feasible also in patients 60–70 years of 
age, with all four patients in this age group receiving the sched-
uled therapy within a total delay of <2 weeks. The haematolo-
gical toxicity was severe but manageable, with 55% of the 
courses followed by febrile neutropenia. Eighty-nine per cent 
of the patients experienced febrile neutropenia and 68% of the 
patients were in need of platelet transfusions any time during 
therapy. Seven patients had one or two episodes with bacterio-
logically documented sepsis, but no deaths due to infection 
during neutropenia were observed.
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MmCHOP</th>
<th>MmCHOP+HDT</th>
<th>BFM</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>13</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>4</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Age, years, median (range)</td>
<td>30 (15–44)</td>
<td>31 (15–56)</td>
<td>36 (17–69)</td>
</tr>
<tr>
<td>Follow-up, months (range)</td>
<td>218 (190–247)</td>
<td>127 (71–179)</td>
<td>49 (13–80)</td>
</tr>
<tr>
<td>Burkitt’s lymphoma</td>
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<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Burkitt-like lymphoma</td>
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<td>3</td>
<td>6</td>
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<tr>
<td>Stage I</td>
<td>4 [0]</td>
<td>4 [0]</td>
<td>4 [2]</td>
</tr>
<tr>
<td>Stage II</td>
<td>1 [1]</td>
<td>3 [0]</td>
<td>7 [1]</td>
</tr>
<tr>
<td>Stage III</td>
<td>1 [0]</td>
<td>0</td>
<td>1 [0]</td>
</tr>
<tr>
<td>Stage IV</td>
<td>7 [0]</td>
<td>10 [3]</td>
<td>7 [3]</td>
</tr>
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<td>IPI score &lt;1</td>
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<td>7 [0]</td>
<td>9 [2]</td>
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<td>IPI score &gt;1</td>
<td>8 [0]</td>
<td>10 [3]</td>
<td>10 [4]</td>
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</table>

*Numbers in brackets: Burkitt-like lymphoma.
BFM, German Berlin–Frankfurt–Munster regimen; ECOG, Eastern Cooperative Oncology Group; HDT, high-dose therapy; IPI, International Prognostic Index; LDH, lactate dehydrogenase; MmCHOP, doxorubicin-based chemotherapy supplemented with intravenous and intrathecal methotrexate.

Table 2. Outcome according to treatment period

<table>
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<tr>
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<tbody>
<tr>
<td>No. of patients</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Overall survival, 5 years (%)</td>
<td>23</td>
<td>71</td>
</tr>
<tr>
<td>Projected 5-year BL/BLL-free survival (%)</td>
<td>31</td>
<td>71</td>
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<tr>
<td>Dead of disease</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Alive</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Complete remission obtained</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Early death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Initial tumour failure</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Death unrelated to BL/BLL</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>CNS progression or relapse</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

BFM, German Berlin–Frankfurt–Munster regimen; BL/BLL, Burkitt’s/Burkitt-like lymphoma; CNS, central nervous system; HDT, high-dose therapy; MmCHOP, doxorubicin-based chemotherapy supplemented with intravenous and intrathecal methotrexate.

Response and survival

Outcome data are presented in Table 2. Seven of 13 (1982–1987) and 12 of 17 (1987–1994) patients obtained CR after MmCHOP induction therapy and 14 of 19 patients after BFM-based therapy. All patients who obtained CR to MmCHOP + HDT or BFM are continuously disease free from BL/BLL. Two patients receiving BFM therapy died within a week of diagnosis in a mixed pattern of acute tumour cell lysis syndrome and infection. Of the three patients who did not achieve CR after initial BFM treatment, one patient received HDT, but eventually died of lymphoma. One patient treated according to the BFM-based protocol was diagnosed with a peripheral T-cell lymphoma 4 years after the diagnosis of BL and died from the T-cell lymphoma with no evidence
of relapsed BL in tumour tissue. The number of patients in each treatment group with CNS progression or CNS involvement at relapse is also given in Table 2.

The projected 5-year PFS rates are 30.8% (95% CI 57–10%; MmCHOP), 70.6% (MmCHOP + HDT) and 73.2% (BFM) (Figure 2) and the projected 5-year overall survival rates for the three treatment groups are 23.1% (MmCHOP), 70.6% (MmCHOP + HDT) and 64.5% (BFM) (Figure 3). Excluding patients treated with only MmCHOP, the projected 5-year PFS by IPI score was 87.5% for IPI <1 and 60% for IPI score >1, and there was no difference in outcome between BL and BLL (74.0% and 66.7%). For the patients who were aged >40 years and treated after 1987 (n = 16) the projected 5-year PFS was 62.5%.

**Discussion**

In this single institution analysis covering a time period of 20 years, we have compared three treatment regimens for BL/BLL in patients 15–70 years of age. The outcome is superior for patients who received either BFM-based therapy or MmCHOP + HDT compared with patients who were only given MmCHOP. One has to take into consideration that improved supportive care may partially explain the inferior results from the first treatment period. However, none of the patients from that treatment period died from treatment complications. All patients who obtained a CR on BFM-based therapy or MmCHOP + HDT are continuously disease free.

The treatment results obtained during the last two decades from the use of multiagent chemotherapy regimens for children with BL or BLL is a major achievement [7–12]. In addition, promising results for adult patients including those with advanced disease have been reported from several groups [9, 18–21]. Soussain et al. [18] reported on 65 adult patients with BL or Burkitt’s acute leukaemia who were treated with a paediatric intensive protocol. With a median follow-up of 57 months, the 3-year overall survival rate was 74%. Mead et al. [19] have comparable results from an international phase II study for adult patients with a similar design employing alternating blocks of intensive chemotherapy. Magrath et al. [9], using a protocol designed for paediatric patients, reported that all 20 adult patients remained alive and free of disease with a median follow-up of 32 months.

There have been very few reports of HDT with autologous stem-cell support in BL and no randomised study reporting treatment results of HDT versus conventional multiagent chemotherapy. The 13 patients transplanted in first CR after initial treatment according to an LMB protocol in the Soussain series [18] did less well than the rest of the patients reported. The data from the EBMT registry [6] showed a 2-year actuarial PFS of 72% for 70 adult BL patients treated in first CR compared to 37% for patients with chemo-sensitive relapse (≥2 CR). Our results with MmCHOP + HDT in BL are promising, with no relapses or toxic deaths. However, our results reported here may be skewed due to the inclusion of patients with stage I disease (four patients). Those patients were, in retrospect, likely to be cured with conventional chemotherapy.

All patients, except one given MmCHOP + HDT, received a purged graft. Few studies have examined in vitro purging techniques for BL or BLL [22], and the question whether purging of the autograft is beneficial for patient outcome remains unclear. Most of the clinical studies in lymphoma patients treated with HDT and purged bone marrow have included tumours of all histology grades; thus the benefit of purging in the few included adult BL patients in these studies could not be evaluated. Recently, a study from the EBMT revealed that purging did not affect engraftment or overall survival [23].

Compared with results from recent studies, the outcome in our analysis, both with the BFM-based regimen and with MmCHOP consolidated with HDT, was satisfactory. Consolidation with HDT after BFM-based therapy is unlikely to improve survival. Although long-term toxicity of the BFM regimen may prove considerable, considerations of documented toxicity may favour the use of BFM-based therapy compared with MmCHOP plus HDT. First, myeloablative therapy is associated with a distinct risk of developing myelodysplasia [24, 25]. Secondly, the prescribed cumulative dose of doxorubicin is much higher with eight courses of CHOP compared to...
the BFM regimen (400 mg/m² versus 100–150 mg/m²). Younger patients are considered vulnerable to doxorubicin-induced cardiotoxicity at doses <300 mg/m² [26]. Thirdly, HDI may be associated with a higher risk of infertility compared to intensive conventional regimens [27], although an inferior chance of childbirth after HDI compared to conventional chemotherapy could not be confirmed in a recent French study [28]. Based on the similar treatment outcome, the favourable long-term toxicity of BFM chemotherapy and the high economic costs of HDI, we consider BFM chemotherapy as the current standard treatment for BL/BLL in patients up to 70 years of age.

Biologically, it is interesting that consolidating a remission after primary CHOP-like chemotherapy for BL with HDI yields a survival benefit while the same has been difficult to demonstrate for diffuse large B-cell and peripheral T-cell lymphomas [29, 30]. Possibly, the daily intensive high-dose cytotoxic and/or radiotoxic therapy for five to six consecutive days is of special value for tumours where close to 100% of the tumour cells are in the cell cycle. The recommended BL therapies, of which the BFM-based regimen is one example, take advantage of the same principle by giving chemotherapy in blocks of five to seven consecutive days. Such therapies may kill virtually all tumour cells as they go through the cell cycle within that time frame.

In conclusion, CHOP/methotrexate-based chemotherapy consolidated with HDI as well as short intensive BFM-based therapy without consolidation produce similar results with significant, but feasible toxicity in patients with BL/BLL up to 60 (70) years. The outcome is superior to CHOP-based regimens strengthened with CNS prophylaxis (MmCHOP).

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