Eighty-one percent event-free survival in advanced Burkitt’s lymphoma/leukemia: No differences in outcome between pediatric and adult patients treated with the same intensive pediatric protocol


1Department of Hematology, 2Department of Pediatrics, University of Verona School of Medicine, Verona, Italy

Summary

Background: Advanced Burkitt’s lymphoma (BL) has an extremely poor prognosis in adults. With a previous protocol including CNS prophylaxis, 40% of our adult patients achieved CR and only 13% became long survivors. In 1988, following this poor experience, we adopted a very intensive pediatric-derived protocol.

Patients and methods: Twenty-one consecutive patients, 8 adults (median age 35, stage III: 1; IV: 7; leukemias: 6) and 13 children (median age 10, stage III: 8; IV: 5; leukemias: 4) were treated with the same protocol (POG 8617), based on alternate two-phase cycles with sequential high-dose CTX, VCR, ADM + CNS chemoprophylaxis (phase A) and HD MTX + HiDAC (phase B). Adults received 6 cycles, children 8; i.t. prophylaxis in phase B was omitted in adults.

Results: Twenty of 21 (95%) patients achieved CR (adults 100%, children 92%). Two patients died early; 2 relapsed at 4 and 9 months. With a median follow-up of 28 months (4-96), 17 patients (81%) are event free (adults 75%, children 85%). Severe infections affected 62% of adults and 15% of children.

Conclusions: (1) The prognosis of adult advanced BL definitely improved with this intensive protocol. (2) There were no differences in outcome between adults and children. (3) Outcome of lymphoma and leukemia was similar. (4) Severe infections occurred frequently in adults. This intensive pediatric protocol requires a careful supportive therapy.

Key words: Burkitt’s lymphoma/leukemia, intensive pediatric treatment

Introduction

Burkitt’s lymphoma (BL) is more common in children than in adults. The disease is characterized by a very rapid course, frequent bone marrow, central nervous system, extranodal involvement, and bulky abdominal masses. It is rapidly fatal unless very intensive therapies are employed. Very good results both in terms of CR and EFS have been reported in children [1-7]. The prognosis of BL in adults is still poor, particularly in patients with advanced stage (bone marrow or CNS involvement) disease or leukemia (8-13). The outcome of adult lymphoma patients has been only recently improved with the adoption of intensive pediatric protocols [14-17]. An intensive, short-term pediatric protocol has been used in adults with Burkitt’s leukemia from the German Cooperative Group [18], obtaining CR ranging between 63% and 74% and a long-term probability of leukemia-free survival of about 50%. Similar results are reported by other groups.

Our previous experience in BL/leukemia has been disappointing: lymphoma patients treated with antracyclin-containing regimens and CNS i.t. prophylaxis, and leukemia patients treated with an ALL-designed protocol, became long survivors only in 13% of the cases. Based on these poor data, since 1988 we started to treat adults with advanced BL or leukemia with a very intensive short-term pediatric protocol.

The plan of therapy was based on high-dose sequential CTX associated with VCR, ADM, and i.t. prophylaxis (cycle A), followed by HD MTX combined by HiDAC (cycle B). This protocol was originally designed for children by the Pediatric Oncology Group (POG), and we modified it for use in adults affected by advanced Burkitt’s lymphoma or leukemia. The adult treatment did differ from the pediatric one by the omission of i.t. in cycle B, and by a reduced number of cycles (6 instead of 8) for adults.

We report here the encouraging results with very high CR rates and improved EFS observed in 21 consecutive patients, 8 adults and 13 children, all with advanced Burkitt’s lymphoma or Burkitt’s leukemia.

Patients and methods

Objective of the study

Our objective was to improve the outcome of adult and pediatric patients affected by advanced BL (Murphy stage III or IV) or Burkitt’s leukemia.
Treatment schedules are shown in Figure 1. The patients were treated with the pediatric protocol POG 8617. Modifications for adults were done (see later).

**Cycle A**
Consisted of high-dose sequential cyclophosphamide (300 mg/sqm i.v. every 12 hours for 6 total doses; days 1-3, followed by VCR (1.4 mg/sqm, days 4 and 11) and ADM (50 mg/sqm, day 4).

**CNS prophylaxis**
During cycle A patients received intrathecal ara-C (50 mg) daily for 3 days (1-3 and 11); i.t. MTX (12 mg) was done at days 4 and 11.

**Supportive care guidelines**

**Hydration**
It is most critical to maintain a brisk urine flow prior to and during the first few days of tumor lysis. This may pose a major challenge, as these patients frequently present with elevated uric acid levels and/or renal infiltration by blast cells. All patients receive hydration (at least 3000 ml/m² per day), allopurinol (200 mg/m² PO) or uricase 1000 U e.v., and alkalinization to maintain urine pH > 6.5. Furosemide was used if urine flow was inadequate. Parenteral nutrition via central line was not started before all fluid and electrolyte problems had stabilized.

**Transfusion**
packed red blood cells were given when clinically indicated. All patients received platelet transfusion at the first sign of bleeding. In addition, platelets were transfused prophylactically for counts less than 10,000 to 20,000/μL. All blood was irradiated and filtered.

**Bone marrow transplantation**
No patients received autologous or allogeneic bone marrow transplantation in first CR, or other types of consolidation therapy. Only one pediatric patient received autologous bone marrow transplantation in second CR at 16 months from the diagnosis. He died from progression of disease 3 months later.

**Criteria for response**
CR was defined as disappearance of all clinical signs and symptoms of disease and negative imaging; normal bone marrow (morphology, immunocytochemistry) was required. Remission status was evaluated after each cycle in all cases.

**End points**
Overall survival (OS) was calculated from the beginning of therapy to the date of the last review (25 May 1995) or death of all entered patients. EFS was determined from the date of initiation of therapy to the date of the last observation without events or to relapse or death from any cause. The probabilities of OS and EFS were computed by the Kaplan-Meier method. The univariate comparison between survival curves was performed by the log-rank test. The maximum follow-up was 96 months. The median follow-up was 28 months (range 4-96+).

**Patient accrual**
From May 1988 to October 1995, 21 consecutive patients (adult 8, children 13, male 17, female 4) observed respectively in the Hematologic Department or Pediatric Onco-Hematologic Unit of the Verona University entered the study.
Table 1. Clinical characters at diagnosis

<table>
<thead>
<tr>
<th>Patients enrolled</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td>6/2</td>
<td>11/2</td>
</tr>
<tr>
<td>Median age</td>
<td>35 (19–64)</td>
<td>10 (4–14)</td>
</tr>
<tr>
<td>Murphy stage III</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Murphy stage IV</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Burkitt's leukemia</td>
<td>6/8 (75%)</td>
<td>4/13 (31%)</td>
</tr>
<tr>
<td>Median LDH</td>
<td>1880 (165–12,000)</td>
<td>764 (104–3715)</td>
</tr>
</tbody>
</table>

Lymphadenopathy

<table>
<thead>
<tr>
<th>Other sites</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinopharynx</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Mediastinum</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Gut</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Liver, pancreas</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Kidney</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Skeletal</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Epidural mass</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Parotid</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Orbital cavity</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Testis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CNS+</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Some patients had more than one involved site.

Clinical results

<table>
<thead>
<tr>
<th>Patients</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>8/8 (100%)</td>
<td>12/13 (92%)</td>
</tr>
<tr>
<td>Early deaths</td>
<td>0/8</td>
<td>1/13 (8%)</td>
</tr>
<tr>
<td>Death in CR</td>
<td>1/8</td>
<td>-</td>
</tr>
<tr>
<td>Relapses</td>
<td>1/8 (12%)</td>
<td>1/12 (8%)</td>
</tr>
<tr>
<td>Patients event-free</td>
<td>6/8 (75%)</td>
<td>11/13 (84%)</td>
</tr>
<tr>
<td>Severe infections</td>
<td>5/8 (62.5%)</td>
<td>2/13 (15%)</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>24 (7–93+)</td>
<td>43 (6–96+)</td>
</tr>
</tbody>
</table>

Some patients had more than one involved site.

Results

The main clinical characters at the diagnosis are reported in Table 1.

Therapy

Overall, the planned cycles of therapy were administered in 17/21 patients (81%). The 6 proposed cycles could be given in 6/8 adults. Reasons for not completing the cycles were toxic death (1) and early relapse (1). The time for completing the cycles in adults who received all 6 cycles was 123 days (range 106–138). The 8 proposed cycles in children could be given in 12/13 (92%). One had rapid disease progression. The median time for completing the cycles in children was 140 days (range 124–166).

Clinical results

Overall 20/21 (95%) patients achieved CR. No differences in CR rate were observed between adults (100%) and children (92%). A pediatric patient died early owing to disease progression. An adult patient died after the CR achievement because of a multiresistant Pseudomonas aeruginosa septicemia. (See Table 2.)

Overall survival

The probability of OS is 81% after a median follow-up of 28 months. The last death occurred at 19 months after the diagnosis.

Event-free survival

The median EFS has not been reached and the probability of EFS for all entered patients is 81% after a median follow-up of 28 months (Figure 2). The probability of EFS is 75% for adults and 85% for children ($P = 0.604$). We did not observe differences between the two age groups (Figure 3), nor were differences observed between patients with advanced Burkitt's lymphoma or leukemia ($P = 0.898$) (Figure 4).
Relapse: Time and location

The two relapses both occurred early: one adult patient with Burkitt's lymphoma relapsed at 4 months (CNS relapse, followed by BM relapse), one child with Burkitt's leukemia at 9 months. Both patients died a few months later owing to disease progression.

Toxicities

Myelotoxicity
All patients had profound neutropenia (<200 PMN/ul) after chemotherapy. Severe infections were frequent in adults (62.5%), being mostly Gram-negative bacteremia (5 patients, 8 episodes, in 2 cases complicated by septic shock); a 53-year-old patient had a mycotic vertebral lesion that was cured after prolonged antifungal therapy. Among children, only 15% had severe Gram-negative bacteremia.

Neurological toxicity
All cases were observed in adults. One patient had seizures after the first phase B cycle; he was treated with anticonvulsants, and no neurological complications were observed after subsequent cycles; after VCR, one patient had peripheral neuropathy and one prolonged constipation.

Hepatic toxicity
All cases were mild and transient.

Nephrotoxicity
One adult patient had transient acute renal failure owing to tumor lysis syndrome after the first cycle.

Use of G-CSF

G-CSF became available during the study. Overall it was employed in 9/21 patients (43%). One of 4 patients treated with G-CSF and 4/4 without G-CSF had severe infections, one fatal. The median time to complete 6 cycles in adult patients who received G-CSF was 117 days (range 106–122); the median time in patients without G-CSF was 129 days (range: 125–138). Five of 13 children received G-CSF, and they did not have severe infections; in the 8 without G-CSF, severe infections occurred in 2 (25%). The median time to complete the CT in children with G-CSF was 132 days (124–166); without G-CSF, 146 days (135–166).

Discussion

Burkitt's lymphoma and leukemia are highly aggressive diseases which can demonstrate remarkable sensitivity to cytotoxic antitumor therapy. Indeed, the use of intensive chemotherapy for Burkitt's lymphomas and leukemias has yielded very gratifying results in children with prolonged EFS and a substantial cure rate [1–7]. Until recently, the results in adults with these B-cell malignancies have been less satisfying. However, with use of intensive chemotherapy regimens originally designed for the pediatric population, some investigators have reported the achievement of a long-term EFS in roughly 50%–60% of adults as well [12, 14–17]. These encouraging results of intensive therapy have been observed in adults with highly aggressive L3 (Burkitt's) ALL as well as in those with Burkitt's lymphoma [18].

Owing to the extremely poor results previously observed in adult patients, we started to treat adults with a slightly modified version of a very intensive, short-term pediatric protocol (POG 8617), whose preliminary good results were observed in children at the Pediatric Oncology Unit of our hospital.

The main results of our study are that CR has been achieved in almost all the patients (95%), and that most of the patients (81%) who entered CR became event-free, with an adequate follow-up (median follow-up: 28 months). In all studies, relapses occurred early, and relapse has rarely been observed beyond one year from the CR achievement. Accordingly, the great majority of our patients can be considered off-risk.

Significantly, adults and children experienced similar clinical outcomes in response to this intensive multiagent regimen. These data support the contention that the salutary clinical results in adults relates to the intensity of chemotherapy; careful supportive therapy, in particular, infection management, is a crucial part of the overall therapeutic approach and is especially important in adults, where the rate of serious infections is significantly greater than in the pediatric population, perhaps in part related to a greater propensity to drug-induced mucositis in the adult. In this regard, the use of G-CSF may decrease the incidence and/or severity of serious infections through diverse mechanisms that relate to both bone marrow and mucosal recovery. The decrease in infectious complications may, in turn, facilitate the administration of full-dose intensity of the antitumor regimen.

In our study we did not observe any differences in clinical outcome between Burkitt's lymphoma and leukemia. This lack of difference may relate to several factors,
including the uniformly advanced stage of lymphoma in this patient population (clinically similar to leukemia) and the use of high-dose cytotoxic therapy with a combination of active agents, namely CTX, MTX, and ara-C (HiDAC). The dose and schedule of CTX used in our regimen may permit sustained exposure of a highly proliferative tumor cell cohort to this active agent. The use of high systemic doses of both MTX and ara-C permits the achievement of relatively high drug levels in the CNS, thus preventing CNS relapse, obviating the need for CNS radioprophylaxis, and avoiding the need for intrathecal MTX with the possibility of MTX-related arachnoiditis or myelitis.

The recent results using intensive short-term pediatric protocols equate with those obtained with bone marrow transplantation [19].

Our results as well as those of other authors confirm the importance of the recommendation reported by Philip in a recent editorial of this journal [20] to make the most of the positive pediatric experiences. That approach seems presently the most important way to improve the outcome of adult patients with advanced Burkitt's lymphoma or leukemia, an outcome extremely unfavorable until few years ago.

Note added in proof
While this manuscript was in preparation, excellent results in both adults and children using intensive pediatric-derived protocol 89-C-41 have also been reported by Magrath and coworkers [21]. Of 41 patients treated with protocol 89-C-41, 95% achieved a complete remission; EFS was 92% (80% in 10 patients with extensive bone marrow infiltration). Similar results using the same protocol have been achieved in children at the University of Rome (Dr. Anna Testi, unpublished data).

Acknowledgements
The authors are grateful to Dr. Judith E. Karp (National Cancer Institute, Bethesda, MD, USA) for useful suggestions on preparing the manuscript.

References

Correspondence to:
Dr. Giuseppe Todeschini
Department of Hematology
University of Verona School of Medicine
Ospedale Policlinico
37134 Verona
Italy