Intensive short-term chemotherapy regimen induces high remission rate (over 90%) and event-free survival both in children and adult patients with advanced sporadic Burkitt lymphoma/leukemia

Giuseppe Todeschini,[1]* Massimiliano Bonifacio,[1] Cristina Tecchio,[1] Rita Balter,[2] Giuseppe Carli,[1] Piero Maria Stefani,[3] Fausto Adami,[4] Alberto Zamò,[5] Angelo Paolo Dei Tos,[6] Filippo Marino,[7] Filippo Gherlinzoni,[3] Pierluigi Marradi,[2] Giampietro Semenzato,[4] and Giovanni Pizzolo[1]

The optimal treatment of advanced sporadic Burkitt lymphoma in adults is still a matter of debate. The salutary results of pediatric therapies did open the road for improving the adult outcome. Between May 1988 and March 2009, 71 consecutive patients—46 adults, 25 children—affected by Burkitt lymphoma/leukemia were treated with the same intensive pediatric protocol alternating vincristine, adriamycine and fractionated ciclophosphamide (phase A) with high dose methotrexate and high dose cytarabine (phase B) in four Italian institutions. Eighty-nine per cent of patients were in Stage III–IV or had L3 leukemia. Complete remissions were 67/71 (94.4%), 24/25 (96%) in children, and 43/46 (93.5%) in adults. Toxic deaths were 3/71 (4.2%), all in adults. There were nine relapses (one in children, eight in adults), all but one observed early. After a median observation of 94 months (range 23–275), the Event–Free Survival rate is 92% in children and 71.7% in adults ($P = 0.067$). The 23 more recent adults received also rituximab, without differences in outcome as compared to patients who did not. Our experience confirms that such an intensive pediatric-derived chemotherapy is feasible and improves the long-term outcome of adults with advanced Burkitt lymphoma. Am. J. Hematol. 87:22–25, 2012. © 2011 Wiley Periodicals, Inc.

Introduction

Fifty years after its description [1] the optimal treatment of adult sporadic Burkitt lymphoma/leukemia (BL) still represents a matter of debate [2]. Standard chemotherapy such as CHOP [3] or adult ALL regimens [4] are clearly inadequate for treating BL, with a long term survival ranging from 0 to 30%. By contrast, the employment of intensive pediatric regimens in adult patients determined better results [5–8]. The HyperCVAD regimen, developed at the M.D. Anderson Cancer Center, confirmed a good activity in BL patients. However, the authors observed that patients older than 60 years clearly had an inferior outcome, with a survival rate of only 17% [9]. The addition of Rituximab and the improvement in supportive care measures possibly contributed to the achievement of similar outcomes in older and younger adults [10].

In 1997, we reported a monocentric experience of 21 patients (8 adults and 13 children) treated with the intensive short-term pediatric-derived chemotherapy regimen POG 8617 [11], demonstrating that the outcome in adults was not significantly different than in children [12]. Fourteen years after our original report, we present here the long-term results of the same chemotherapy regimen employed in a multicenter experience recruiting a larger cohort of 71 consecutive BL patients. Of note, 48% of adult patients were older than 40 years and Rituximab was added to chemotherapy in the more recently enrolled adult patients. With a median follow-up of about 8.5 years, we confirm that this intensive pediatric-derived regimen is safe and improves the outcome of adults with advanced BL.

Patients and Methods

Study population. . The study was conducted in four institutions of the Veneto region (Northeastern Italy): University of Verona, Hematology Unit (32 patients) and Pediatric Hematology Oncology Unit (25 patients); Treviso Hospital, Hematology Unit (nine patients) and University of Padua, Hematology Unit (five patients). Twenty-one patients, eight adults, and 13 children were previously reported [12]. All previously untreated patients affected by BL or Burkitt's leukemia were included in the study. No upper age limit was fixed, and patients were enrolled if considered fit for intensive chemotherapy treatment.

Diagnosis and clinical investigations. Three institutional Pathological Departments (Verona, Treviso and Padua) performed and rewieved all the diagnostic specimens. Diagnosis of BL was made on tissue samples showing the typical histological pattern of monotonous proliferation of medium-sized cells with round nuclei, multiple basophilic paracentrally situated nucleoli, multiple cytoplasmic vacuoli, "starry-sky" appearance, extremely high proliferative tumor index (Ki-67 positive >95%) and the presence of pan B-cell antigens and surface Ig expression, according to the criteria used at the time of patients' enrollment. Diagnosis of leukemia was done when more than 25% of blasts with the same phenotypical characters were present in the bone marrow samples or in peripheral blood. Patients underwent standard physical, biochemical, and radiological examination, as described [12].

Treatment. All patients signed an informed consent before study entry and were treated according to the pediatric-derived protocol POG 8617 [11], with minor modifications (see below and Fig. 1). In all centers, the study was conducted with the approval of local ethics committees.

Cycle A consisted of sequential cyclophosphamide (300 mg/sqm i.v. every 12 hr for 6 total doses, days 1–3), followed by vincristine (1.4 mg/sqm, days 4 and 11) and adriamycine (50 mg/sqm, day 4), without steroids. Cycle B consisted of high dose methotrexate (1 g/sqm, continuous i.v. infusion over 24 hr), followed by leucovorin rescue, and high dose ARA-C (3 g/sqm i.v. every 12 hr for 4 total doses, days 2–3).

[1]Department of Medicine, Section of Hematology, University of Verona, Verona, Italy; [2]Pediatric Hematology Oncology Unit, Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy; [3]Hematology Unit, Ca' Foncello Hospital, Treviso, Italy; [4]Department of Clinical and Experimental Medicine, Section of Hematology and Clinical Immunology, Padua University School of Medicine, Padua, Italy; [5]Department of Pathology and Diagnostics, Section of Pathological Anatomy, University of Verona, Verona, Italy; [6]Department of Pathology and Molecular Genetics, Ca' Foncello Hospital, Treviso, Italy; [7]Department of Medical/Diagnostic Sciences, Section of Anatomic Pathology, University of Padua, Padua, Italy

Conflict of interest: Nothing to report.

*Correspondence to: Prof. Giuseppe Todeschini, Department of Medicine, Section of Hematology, Azienda Ospedaliera Universitaria Integrata of Verona, P.le L.A. Scuro, 10, Verona 37134, Italy. E-mail: giuseppe.todeschini@univr.it

Received for publication 5 September 2011; Accepted 10 September 2011

Am. J. Hematol. 87:22–25, 2012.

Published online 13 September 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/ajh.22189

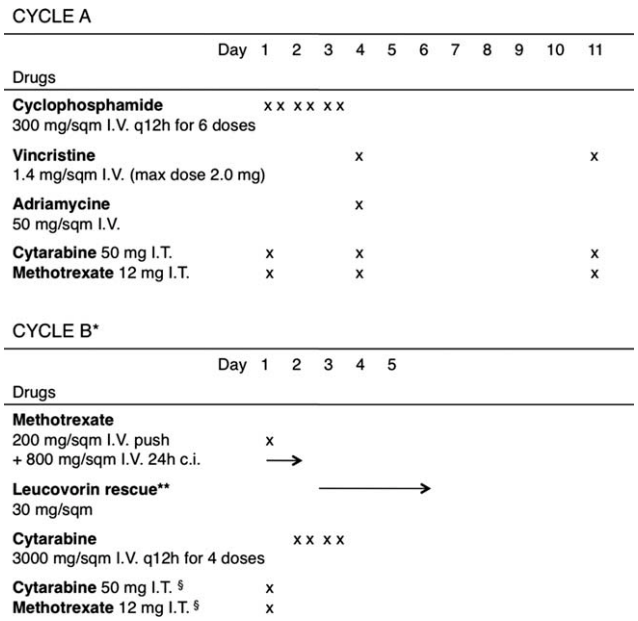

Figure 1. Protocol scheme. I.V.: intravenous. I.T.: intrathecal. *Cycle B is administered as soon as there is recovery of bone marrow function (neutrophils + phagocyte count >500/μL and platelets >100,000/μL). **Leucovorin rescue starts 18 hr after completing the MTX infusion and should be continued until the plasmatic level of MTX is <0.1 μM. §Only in children.

Three complete cycles (3 phase A and 3 phase B alternated) were planned for adults, four cycles for children. Elderly patients (age >65 years) were planned to receive two cycles. For adult patients in first complete remission (CR) no consolidation or maintenance therapy was adopted.

CNS prophylaxis. During cycle A patients received double intratecal (i.t.) medication (cytarabine 50 mg, methotrexate 12 mg) at days 1, 4, and 11. During cycle B, the i.t. planned for children was omitted in adults.

Supportive measures. Each cycle was administered when neutrophils + phagocyte count was over 500/μL and platelets over 100,000/μL. In presence of active infection, the cycle was postponed. From 1994, G-CSF was routinely used in children and in adults, starting 24 hr after the end of chemotherapy infusion and stopping when neutrophil + phagocyte count reached 500/μL.

To prevent tumor lysis syndrome, all patients receive hydration (at least 3,000 mL/sqm per day), oral allopurinol or i.v. rasburicase, and alkalinization to maintain urine pH >6.5. Furosemide was used if urine flow was inadequate.

Rituximab. Since Rituximab became available for treatment of adult B-cell high-grade lymphomas from November 2002, the 23 most recently enrolled adult patients received rituximab at standard dosage (375 mg/sqm) the day before each cycle. Rituximab was omitted before the first cycle in patients with a high disease burden to minimize the risk of tumor lysis syndrome. Children never received rituximab.

Stem cell transplantation. No patients received autologous or allogeneic bone marrow transplant in first CR.

Criteria of 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 by clinical and/or radiological examination after each cycle in all cases. Positron-emission tomography (PET) scan became available only in the more recent years so it was not routinely used to assess remission status. Therefore, we utilized the criteria of response according to Cheson et al. [13]. When CR occurred after the first POG cycle (phase A + B), the definition of "early CR" was adopted. After treatment completion all patients were regularly followed: in particular a complete clinical and radiological (ecotomography and CT scan) assessment was performed 4 and 12 months after the end of chemotherapy and then a clinical evaluation was done at least once a year.

Statistical analysis. Overall survival (OS) was calculated from the beginning of therapy to the date of the last review (December 2010) or death from any cause. Event-free survival (EFS) was calculated from the date of the start of chemotherapy to the last observation without events, relapse, or death from any cause. The probabilities of OS and EFS were computed by the Kaplan–Meier method. The comparison between survival curves was made by the log-rank test. The comparison between adults and children, and between adult patients who received rituximab and who did not, was made by the Fisher exact test.

TABLE I. Patients' Characteristics

	<15 yrs (n = 25)	P^*	15–40 yrs (n = 24)	>40 yrs (n = 22)
Age years (median)	6 (3–14)		26 (17–39)	53 (41–77)
Male/female	19/6		16/8	15/7
Ann Arbor Stage III-IV	23 (92.0)	NS	20 (83.3)	20 (90.1)
Bulky disease	9 (36.0)	NS	13 (54.2)	9 (41.0)
Extranodal disease	22 (88.0)	NS	17 (70.8)	15 (68.2)
SNC involvement	3 (12.0)	NS	4 (16.7)	3 (13.6)
Leukemic presentation	4 (16.0)	0.034	10 (41.7)	10 (45.4)
Bone marrow involvement	6 (24.0)	0.044	11 (45.8)	12 (54.5)
Increased LDH serum levels	10 (40.0)	0.011	18 (75.0)	15 (68.2)

* P value is calculated between children and adults (>15 years). There are no differences between younger (i.e., 15–40 years) and older (>40 years) adults.

Results

Patients' characteristics

The main clinical characters at diagnosis are reported in Table I. There were no significant differences between adult patients enrolled before November 2002 and treated without Rituximab, and patients enrolled after that time and treated with immunochemotherapy (data not shown).

Treatment

As described above, a first group of 10 children, enrolled from 1988 to 1994, were planned to receive four cycles of therapy. One patient received only 1.5 cycles and had progressive disease (PD); all the other nine children completed the treatment. The second group comprised 15 children, enrolled from 1994 to 2005, who were treated with three complete POG cycles.

In the majority of adults the planned treatment was completed. The main reasons for not completing the therapy were toxic deaths and PD (two and three patients, respectively). Two patients with Stage I, non-bulky disease received two cycles. Two patients aged >65 completed the planned therapy: one of them is alive and disease-free after 4 years and the other died of acute myocardial infarction 5 months after completing the treatment, while in CR.

Results

Overall 67/71 (94.4%) of patients achieved the CR, 24/25 (96%) in children and 43/46 (93.5%) in adults. One child progressed during the treatment and rapidly died. Among adults, one patient had a early toxic death, before assessment of response, and two patients did not obtained any type of remission and died of disease.

There were no toxic deaths in children. The fatal toxicities in adults were three: deaths were due to multi-organ failure (one), bacterial pneumonia (one), and acute myocardial infarction (one).

Relapses were nine, one in children and eight in adults. All but one occurred early, with a median time to relapse of only 4 months. One adult patient had an unexpectedly late relapse, 9 years after diagnosis and died 14 months later due to PD (Table II).

Time to response

Children had more rapid response, all but two (23/25, 92%) achieving early CR. One child obtained the CR after the second cycle. In adults, 33/46 patients (71.7%) had an early CR, 10/46 (21.7%) achieved CR after two or more POG cycles and 3/46 (6.5%) did not obtain CR. This difference is not statistically significant.

Stem cell transplantation

After relapse one pediatric patient received autologous transplant and one adult underwent allogeneic stem cell

TABLE II. Results of Treatment: Comparison Between Age Groups

	All patients ($n = 71$)	<15 yrs ($n = 25$)	15–40 yrs ($n = 24$)	>40 yrs ($n = 22$)	P*
Alive in CCR	56 (78.9)	23 (92.0)	18 (75.0)	15 (68.2)	NS
Toxic deaths	3 (4.2)	0	1 (4.2)	2 (9.1)	NS
Relapsed and dead	12 (16.9)	2 (8.0)	5 (20.8)	5 (22.7)	NS

*P value is calculated between children and adults (>15 years). There are no differences between younger (i.e., 15–40 years) and older (>40 years) adults.

transplant from a sibling donor. Both rapidly progressed and died.

Survival

After a long follow-up, the EFS in children is 92% (median follow-up 157 months, range 67–275) and in adults is 71.7% (median follow-up 67 months, range 23–268), that is not statistically different ($P = 0.067$). The probability of EFS is 75% for adults aged between 15 and 40, and 68.2% for adults older than 40 years, without statistical difference (Fig. 2).

Role of rituximab

Fifty percent of adults received Rituximab in addition to chemotherapy. There were no differences in the probability of CR achievement, relapse, and EFS. In particular, the EFS is 69.6% and 73.9% for patients receiving or not Rituximab (P = ns).

Discussion

This is a large series of patients who were treated homogeneously, independently by age, with the same pediatric-designed protocol and observed for a very long follow-up period.

The CR rate was very high (93.5% in adults and 96% in children). This translated in a remarkable long-term cure rate, with an overall EFS of 78.9% after a median follow-up of about 8 years, without significant differences between children and adults. This results appear notable, since the large majority of patients (89%) were in advanced stage or leukemic phase. Another short intensive chemotherapy regimen obtained an EFS of 72.7%, but half of patients were in Stage I–II [8]. The results of other various short duration/dose intensive regimens appear not superior, with EFS ranging from 50 to 70% [6,7,14,15].

In a recent prospective clinicopathological study Mead et al. highlighted the importance of a strict pathologic definition of BL, based on immunophenotypic and genetic criteria, since the 2-years PFS of patients treated with a short intensive chemotherapy regimen (CODOX-M/IVAC) is superior in BL than DLBCL, although without significant difference (64% vs. 55%, respectively) [16]. Due to the long accrual time of our study, diagnosis of BL was made according to the diagnostic criteria used at the time of study entry and we cannot rule out that some adult cases could be now indicated as B-cell lymphomas, unclassified, intermediate between DLBCL and BL. However, our study population presented a homogeneous high-risk profile and was uniformly treated so we believe that this retrospective experience could provide some informations about the effectiveness of this treatment in high-risk, aggressive B-cell lymphomas beyond the strict diagnostic definition.

Patients older than 40 years were under-represented in the main published series, and their outcome was significantly inferior compared with younger patients. A pooled analysis of various published trials showed that the median OS at 2 years for all patients treated with short-duration therapy was 71%, and for patients older than 40 years was only 39% [17]. In our series about 50% of adults were older than 40 years. All adult patients (aged 15–40 and >40 years) were characterized by a more unfavorable disease than children (significantly more frequent bone marrow involvement and leukemic presentation): they achieved less promptly the CR, and had a higher relapse rate. This "more unfavorable" adult disease appears independent of the known reduced tolerance to chemotherapy in adults. In fact, we observed a low toxic mortality (6.5%) in adults in spite of the advanced disease and chemotherapy intensiveness, thus indicating that this intensive pediatric-derived regimen can be safely used in adults also, if a vigorous supportive care is provided.

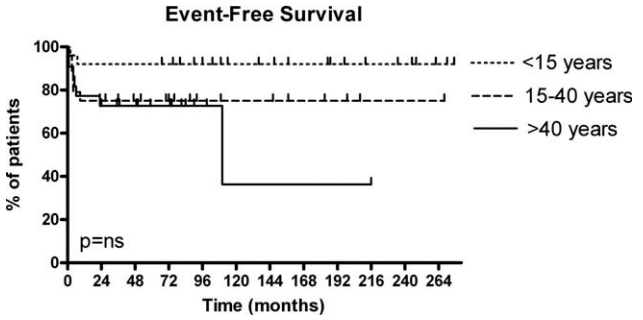

Figure 2. Event-free survival plots of the 71 patients according to their age group.

The incidence of CNS involvement was not different between children and adults and did not influence the outcome: in particular, the probability of PFS in adults was 71.4% vs. 71.8% for patients with or without CNS disease. It is likely that these results may be attributable to the use of high doses of MTX and ARA-C.

Relapse was the main cause of failure. Relapses occurred early, within a median time of 4 months from CR achievement and tended to be more frequent in adults. After relapse, patients were treated, according to their performance status and clinical conditions, with a range of options up to autologous or allogeneic stem cell transplantation. Notably, no patient could be rescued and death occurred in few weeks, suggesting that the outcome of patients unresponsive to first-line chemotherapy is usually rapidly fatal and virtually no rescue possibilities exist. This observation suggests that any curative effort should be done with intensive treatment in the early phase of the disease. In our experience, the use of stem cell transplantation appears not to be necessary in first line and uneffective as rescue after relapse/progression of the disease.

As far as Rituximab use, we failed to observe difference in outcome according to its employment. This could depend on the limited number of treated patients and on the retrospective nature of this comparison. In a study from M.D. Anderson Cancer Center, patients who received Rituximab had a definitely better outcome as compared with historical controls [10]. However, the excellent results achieved in children who never received rituximab could rise questions about the role of rituximab in these extremely high kinetics lymphomas, when an intensive chemotherapy is done. On the other hand, the addition of Rituximab in adults could improve the chemotherapy results due to their intrinsic more unfavorable disease.

In conclusion, this multi-institutional study on a large cohort of patients and a very long follow-up confirms 14 years later our previous mono-institutional experience [12]. The results achieved in this rare aggressive lymphoma with the present and other similar intensive regimens constitute one of the major successes of chemotherapy. Our study confirms that a pediatric-oriented approach provides significant improvement also in adult and in fit older patients.

References

1. Burkitt D. A sarcoma involving the jaws in African children. Br J Surg 1958;46:218–223.
2. Perkins AS, Friedberg JW. Burkitt lymphoma in adults. Hematology Am Soc Hematol Educ. Program 2008;341–348.
3. Smeland S, Blystad AK, Kvaloy SO, et al. 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. Ann Oncol 2004;15:1072–1078.
4. Hoelzer D, Ludwig WD, Thiel E, et al. Improved outcome in adult B-cell acute lymphoblastic leukemia. Blood 1996;87:495–508.
5. Magrath I, Adde M, Shad A, et al. Adults and children with small non-cleaved-cell lymphoma have a similar excellent outcome when treated with the same chemotherapy regimen. J Clin Oncol 1996;14:925–934.
6. Mead GM, Sydes MR, Walewsky J, et al. An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: Results of United Kingdom Lymphoma Group LY06 study. Ann Oncol 2002;13:1264–1274.
7. Rizzieri DA, Johnson JL, Niedzwiecki D, et al. Intensive chemotherapy with and without cranial radiation for Burkitt leukemia and lymphoma: Final results of Cancer and Leukemia Group B Study 9251. Cancer 2004;100:1438–1448.
8. Di Nicola M, Carlo-Stella C, Mariotti J, et al. High response rate and manageable toxicity with an intensive, short-term chemotherapy programme for Burkitt's lymphoma in adults. Br J Haematol 2004;126:815–820.
9. Thomas DA, Cortes J, O'Brien S, et al. Hyper-CVAD program in Burkitt's-type adult acute lymphoblastic leukemia. J Clin Oncol 1999;17:2461–2470.
10. Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with Hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer 2006;106:1569–1580.
11. Murphy SB, Bowman WP, Abromowitch M, et al. Results of treatment of advanced-stage Burkitt's lymphoma and B cell (S Ig+) acute lymphoblastic leukemia with high-dose fractionated cyclophosphamide and coordinated high-dose methotrexate and cytarabine. J Clin Oncol 1986;4:1732–1739.
12. Todeschini G, Tecchio C, Degani D, et al. 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. Ann Oncol 1997;8:S77–S81.
13. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. J Clin Oncol 1999;17:1244–1253.
14. Kujawski LA, Longo WL, Williams EC, et al. A 5-drug regimen maximizing the dose of cyclophosphamide is effective therapy for adult Burkitt or Burkitt-like lymphomas. Cancer Invest 2007;25:87–93.
15. van Imhoff GW, van der Holt B, MacKenzie MA, et al. Short intensive sequential therapy followed by autologous stem cell transplantation in adult Burkitt, Burkitt-like and lymphoblastic lymphoma. Leukemia 2005;19:945–952.
16. Mead GM, Barrans SL, Qian W, et al. A prospective clinicopathological study of dose-modified CODOX-M/IVAC in patients with sporadic Burkitt lymphoma defined using cytogenetic and immunophenotypic criteria (MRC/NCRI LY10 trial). Blood 2008;112:2248–2260.
17. Friedberg JW, Ciminello L, Kelly J, et al. Outcome of patients > age 40 with Burkitt lymphoma (BL) treated with aggressive chemotherapeutic regimens: Results from the International Burkitt Lymphoma Collaborative Group. Blood (ASH Annual Meeting Abstracts) 2005;106:Abs#928.