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# Treatment of Poor Prognosis Burkitt's Lymphoma in Adults with the Société Française d'Oncologie Pédiatrique LMB Protocol—A Study of the Federation Nationale des Centres de Lutte Contre le Cancer (FNLCC)

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**14 adult patients between 16 and 50 years old with small non-cleaved cell lymphoma (Burkitt's lymphoma) were prospectively treated from 1982 to 1990 with the LMB protocols of the Société Française d'Oncologie Pédiatrique (SFOP). No HIV-positive patients were included. All patients had extensive disease with bad prognosis factors, i.e. 10 patients had Murphy stage III and 4 had stage IV with bone marrow involvement. The LMB protocols were characterised by high-dose fractionated cyclophosphamide, high-dose methotrexate (HD-MTX), and cytosine arabinoside. No local or central nervous system irradiation was used. Treatment duration ranged from 5 (LMB 84) to 12 (LMB 81) months. There were no therapy-related deaths. All patients achieved complete remission (CR). 6 patients relapsed between 2 and 30 months following CR. 8 of the 14 patients (57%) are still alive and disease-free after treatment by LMB protocol alone. 2 patients were salvaged with bone marrow transplantation after relapse and a total of 10 out of 14 patients (71%) are disease-free at the time of this report. Our results showed the high curability of advanced Burkitt's lymphoma using a paediatric protocol, even in adult patients. The LMB protocol may be applied to adult patients but requires intensive care during the induction period.**
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## INTRODUCTION

CURE OF advanced aggressive lymphoma was first obtained with the MOPP protocol in 1973, and results were only slightly improved with the CHOP regimens in 1976 [1, 2]. Modern intensive and alternating drug protocols of the second and third generation such as M-BACOD, ProMACE-MOPP, ProMACE-CYTABOM and MACOP-B, for example [1, 3–8] are based since 1980 on the theoretical model of Goldie and Coldman [9] and the putative relationship between dose intensity and efficacy [10, 11]. These protcols produce long-term disease-free survival (DFS) rates of 55–70% with adult patients but results are mainly reported in large cell lymphoma and the superiority of these aggressive protocols are still a matter of debate.

Burkitt's lymphoma is diagnosed in up to 60% of paediatric

*Table 1. Details of the 14 adult patients with Burkitt's lymphoma*

| Center No. | Case No. | Age | Sex | PS | Stage M | Stage AA | Main local | Protocol | Response | CR1 | Relapse | Death | Salvage treatment | Current status |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I | 1 | 17 | F | 4 | III B | IIE | A | LMB84S | CR | | 2.5 | | ABMT MIME×2 BEAM+ABMT | CR 20+ |
| II | 2 | 26 | M | 2 | III B | IIIE | A/N | LMB84L | CR | 70+ | | | | CR 70+ |
| V | 3 | 36 | F | 1 | III B | IIE | A | LMB84L | CR | 70+ | | | | CR 70+ |
| I | 4 | 16 | M | 2 | III B | IIE | A | LMB81 | CR | 1 | 2 | 4 | | died |
| I | 5 | 50 | M | 3 | III A | IIE | A | LMB84S | CR | 1 | 2 | 2.5 | | died |
| I | 6 | 16 | M | 3 | III A | IIE | A | LMB84S | CR | 75+ | | | | CR 75+ |
| I | 7 | 45 | F | 0 | IV BM | IV | A | LMB84L | CR | 75+ | | | | CR 75+ |
| I | 8 | 16 | M | 3 | IV BM | IV | A | LMB81 | CR | 98+ | | | | CR 98+ |
| I | 9 | 26 | M | 2 | IV BM | IV | A | LMB84L | CR | 93+ | | | | CR 93+ |
| IV | 10 | 33 | F | 2 | III B | IIE | A | LMB81 | CR | 2 | 3 | 6 | | died |
| III | 11 | 22 | M | 3 | III B | IIE | A | LMB84S | CR | 40 | 30 | | LMB84+BMT | CR 34+ |
| II | 12 | 24 | M | 2 | III B | IIE | A | LMB84L | CR | 71+ | | | | CR 71+ |
| VI | 13 | 18 | M | 2 | III B | IIE | A | LMB84S | CR | 2 | 2 | 2 | | died |
| VII | 14 | 23 | M | 2 | IV BM/MU | IV | A | LMB84S | CR | 20+ | | | | CR 20+ |

Center: I, Lyon; II, Tours; III, Rennes; IV, Lille; V, Châlon s/S; VI, Besançon; VII, Saint Cloud.
Sex: M, male; F, female. PS, Performance status.
Stage: (M, Murphy; AA, Ann Arbor); BM, bone marrow; MU, multiorgan involvement. Main local; A, abdominal; N, neck region.
Protocol: LMB84S, short arm version; LMB84L, long arm version (see Table 4).
CR, complete response.

lymphoma patients [12, 13] but only in 4–7% of adult patients [14, 15]. Adult Burkitt's lymphoma now occurs more frequently with increasing incidence of HIV infection [16]. Results with adult lymphoma protocols are generally unsatisfactory for the highly aggressive Burkitt's lymphoma, particularly in advanced stage III and IV [16, 17].

Paediatric oncologists were the first to develop more intense and more aggressive chemotherapy protocols and to show that B-cell and T-cell lymphomas need different therapeutic strategies. The LSA2-L2 protocol [18, 19] was mainly active for T-cell lymphomas as well as the NCI-7704 protocol [20] whereas the COMP (CCSG 1983) [21, 22] and the COPAD (Institut Gustave Roussy; Centre Léon Bérard) [12, 23] schedules produced good results mainly in B-cell lymphomas. B-cell lymphoma chemotherapies are generally short-pulsed, and T-lymphoma schedules are much more similar to leukaemia protocols [24–27].

Adult and paediatric patients are generally treated with different protocols but there are some exceptions for young adults with highly aggressive lymphomas, i.e. the NCI-7704 [20] as well as the French LMB protocols are proposed for young adults up to the age of 35.

The LMB protocol was first activated in 1981 by the Société Française d'Oncologie Pédiatrique (SFOP) for advanced stage B-cell lymphoma and modified in 1984 [23, 24, 28–30]. An intensified version was introduced in 1986 for B-cell acute lymphoblastic leukaemia (ALL) and central nervous system (CNS) involvement and also in 1989 for massive bone marrow involvement superior to 70% [29, 30].

The results of the LMB 81/84 protocols with children have been previously published [24, 28, 29, 31]. We will report here on 14 adult patients with Burkitt's lymphoma. Results and toxicity are compared with those achieved with pediatric Burkitt's lymphoma patients as well as with results obtained with protocols for adult advanced aggressive lymphoma.

## PATIENTS AND METHODS

*Patients*

From 1982 to 1990 14 patients (10 men, 4 women) aged between 16 and 50 years (average age 26.3 years) with Burkitt's lymphoma were prospectively included in the LMB protocols and are described in detail in Table 1. 7 patients were treated at

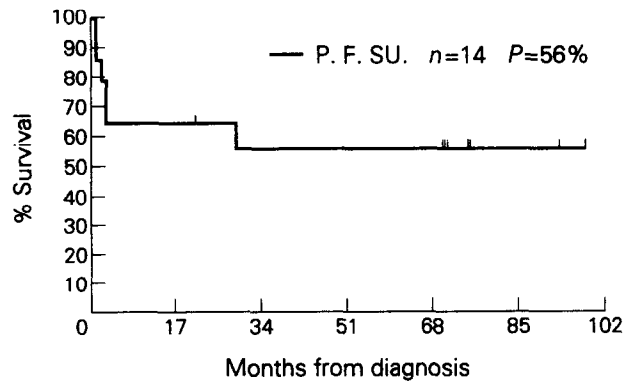


**Fig. 1. Burkitt's lymphoma—14 patients' progression-free survival.**

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the Centre Léon Bérard and 7 in other French centres (Tours, Rennes, Chalon sur Sâone, Lille, Besançon, Saint Cloud). Median follow-up is 59.2 months on 1 April 1992 (range 16–89). No HIV-positive patients were included in this study.

*Pretreatment studies including staging procedures*

Physical examination, full blood count, bilateral bone marrow aspirates and marrow trephine biopsies were always performed, with examination of cerebrospinal fluid (CSF), and pleural and abdominal fluid if available. Imaging procedures were chest X-rays, abdominal ultrasonography and in most patients computer tomography examinations of chest, abdomen and each clinically affected region. Sedimentation rate, fibrinogen, enzyme activity of lactate dehydrogenase (LDH), electrolytes, urea, creatinine, uric acid, liver function tests, total IgE, beta-2-microglobuline, immunoelectrophoresis and serological tests of Epstein–Barr virus (EBV), HIV and hepatitis B were also performed.

*Staging system*

Staging was defined according to the Murphy paediatric classification [31] with the previously published Lyon modifications, i.e. stage III B (extensive multiorgan involvement) or stage III A (other cases) [32]. 2 patients had modified Murphy stage III A, 8 stage III B and 4 stage IV with bone marrow involvement. There were no patients with limited disease and no patients with initial CNS involvement included in this study. Ann Arbor classification of all cases is recorded in Table 1.

*Histological and immunological studies*

All patients had histologically proven small non-cleaved cell lymphoma of the Burkitt type [32]. B-Cell type was proven in all cases by immunological procedures with monoclonal surface immunoglobulins and antigens of the B-cell series defined in all cases [33].

*Treatment*

The LMB 81/84 protocols are described in detail in Table 2. The LMB 81 protocol was used during the 1981–1984 period. The induction part of this protocol is characterised by a low-dose prephase (COP) in order to prevent tumour lysis syndrome followed at days 5–7 and 17–21 by two COPADEM modules where fractionated high-dose cyclophosphamide, vincristine, adriblastine, prednisone and high-dose methotrexate (HD-MTX) were sequentially given. Consolidation was with continuous cytarabine, asparaginase, and HD-MTX alternating with carmustine (BCNU), aracytine, cyclophosphamide and thioguanin (Mini-BACT). Maintenance treatment was performed with four cycles of alternating sequences 1 and 2, in which sequence 1 can be compared with COPADEM and sequence 2 with Mini-Bact at lower doses. In the LMB 84 protocol, doses of cyclophosphamide and vincristine were reduced in the COPADEM 1 module, and asparaginase was suppressed in the CAM cycle ("CYM"). Maintenance therapy was also shortened with a randomisation between only one sequence 1 and Mini-BACT replaced by a second CYM, and a long arm (two cycles of both sequences 1 and 2). Since November 1987 all patients had received the short arm [24, 25].

Treatment duration ranged from 12 months in the LMB 81 to only 5 months in the short arm version of LMB 84. The total doses of adriblastine/cyclophosphamide/methotrexate were 0.36/10.3/21 g/m² in the longest and 0.18/4.3/15 g/m² in the shortest version of the protocol. Spacing between COP and COPADEM 1 was 5–7 days; the second COPADEM module

*Table 2. Details of each sequence of the protocols LMB 81/84*

| | | Day 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|---|
| COP | C | 300‡ | | | | | | | |
| | O | 1 | | | | | | | |
| | P | 60 | 60 | 60 | 60 | 60 | 60 | | |
| | MTX IT* | 15 | | | | | | | |
| COPADEM 1 | C | | 500 | 500 | 500 | | | | |
| | O | | 2§ | | | | | | |
| | P | 60 | 60 | 60 | 60 | 60 | 60 | 60 | |
| | Ad | | 60 | | | | | | |
| | MTX | 3000 | | | | | | | |
| | FA | | 15×4 | 15×4 | 15×4 | | | | |
| | MTX IT | | 15 | | | | 15 | | |
| COPADEM 2 identical but 1000 mg/m² of cyclophosphamide on days 2–4 up to 1989 and 2 mg/m² vincristine on days 1–6 | | | | | | | | | |
| CYM | Ara C† | 100 | 100 | 100 | 100 | 100 | | | |
| | MTX | 3000 | | | | | | | |
| | FA | | 15×4 | 15×4 | 15×4 | | | | |
| | MTX IT | 15 | | | | | | | |
| | Ara C IT | | | | | | 15 | | |
| CAM identical but also 1000 U/kg L-asparaginase on days 2–6 | | | | | | | | | |
| Mini-BACT | BCNU | 60 | | | | | | | |
| | Ara c | 100 | 100 | 100 | 100 | 100 | | | |
| | C | | 500 | 500 | 500 | | | | |
| | TG | 150 | 150 | 150 | 150 | 150 | | | |
| Sequence 1 | MTX | 3000 | | | | | | | |
| | FA | | 15×4 | 15×4 | 15×4 | | | | |
| | O | 1.5 | | | | | | | |
| | C | | 500 | | | | | | |
| | Ad | | 60 | | | | | | |
| | P | 60 | 60 | 60 | 60 | 60 | 60 | 60 | |
| | MTX IT | | 15 | | | | | | |
| Sequence 2 | BCNU | 60 | | | | | | | |
| | Ara C | 100 | 100 | 100 | 100 | 100 | | | |
| | TG | 150 | 150 | 150 | 150 | 150 | | | |
| | Ara C IT | 30 | | | | | | | |

C, Cyclophosphamide; O, vincristine; P, prednisone; MTX, methotrexate; IT, intrathecal; Ad, doxorubicin; FA, folinic acid; Ara C, aracytine; BCNU, lomustine; TG, thioguanine.

*All MTX IT injections with 15 mg hydrocortisone.

†Continuous infusion for 5 days

‡All doses are in mg/m² and administered intravenously except for TG.

§Maximum dose 2 mg.

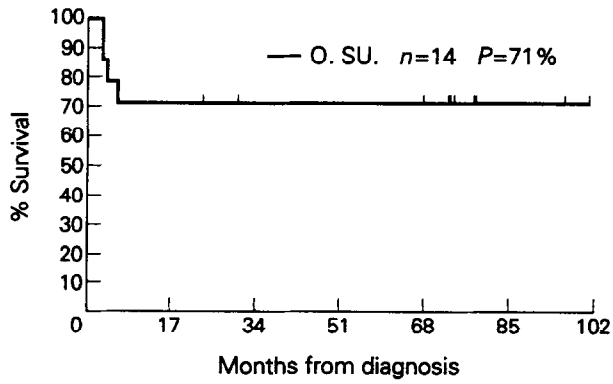


**Fig. 2. Burkitt's lymphoma—14 patients' overall survival.**

was started as soon as white blood cells (WBC) exceeded 3000 and platelet count exceeded 100 000 which was generally achieved at day 17–21. Consolidation cycles followed at day 21 and 42 of the second induction module, and maintenance cycles were administered every 3 to 4 weeks. The different cycles were postponed if WBC was below 3000 and platelet count was below 100 000.

CNS prophylaxis was carried out by HD-MTX infusions and intrathecal injections of methotrexate and aracytin. No radiotherapy was applied either for CNS prophylaxis or for bulky tumour masses.

3 patients received the LMB 81 protocol and 11 the LMB 84 protocol; 6 of whom had the short arm and 5 the long arm of maintenance therapy. Our patients always received the pediatric protocol with the exception of the randomisation of the LMB 84 where they were not eligible and the long arm was used until clear demonstration that the short arm was equivalent [24, 25].

Before starting the COP module and during induction and consolidation chemotherapy alkaline hyperhydration with 3 l/m$^2$ was given. Allopurinol was also given during the first COP and COPADEM modules. Citrovorum factor rescue started 24 h after the beginning of each HD-MTX perfusion by 12 injections of 15 mg/m$^2$ folinic acid every 6 h. MTX blood levels were monitored at 24, 48 and 72 h. Blood counts were taken daily on therapy and twice weekly between courses. Aplasias were treated by association of wide spectrum antibiotics.

*Analysis of response*

Response to therapy was assessed clinically at each cycle, and complete restaging was performed between the two consolidation cycles 10 to 12 weeks after diagnosis with bone marrow biopsies and aspirates, CSF examination and every imaging procedure appropriate to the initial disease site.

Criteria of assessment were survival from the start of treatment and disease-free survival (DFS). For DFS, the events of interest were failures defined as no complete remission, relapse or death. Survival and DFS were computed using the method of Kaplan and Meier [34]. The 2 patients who received salvage therapy after relapse (Nos 1 and 11) were regarded as failures for DFS.

## RESULTS

There were no therapy-induced toxic deaths. Haematological toxicity was important during the induction period: 75% of COPADEM modules were followed by febrile aplasia requiring hospitalisation for broad systemic antibiotic therapy. However, febrile aplasia occurred only after two out of 20 evaluated CYM cycles and after one of seven Mini-BACT cycles. Maintenance cycles did not generally induce major infectious problems. In all cases febrile aplasia was accompanied by a mucositis varying from grade 2 to 4.

Extramedullary toxic problems occurred only sporadically. We observed one case of dysarthria related to HD-MTX (patient No. 9), one case of inappropriate secretion of antidiuretic hormone (patient No. 6), one case of asparaginase-induced imbalance of glucose metabolism (patient No. 7) and one case of tumour lysis syndrome (patient No. 8). All were easily manageable. All 14 patients achieved CR (100%). 6 patients relapsed between 2 and 30 months after the assessment of CR as shown in Table 3. 8 out of the 14 patients are alive without evidence of disease after LMB treatment alone. Disease-free survival obtained with LMB protocols ranges from 20 to 98 months (median 55.5), see Fig. 1. The 2 patients treated with salvage therapy including BMT obtained a persistent CR. Overall survival for all 14 patients is 71% (10/14), as shown in Fig. 2 overall survival time ranges from 22 to 101 months (median 59.2).

## DISCUSSION

Burkitt's lymphoma is one of the most aggressive and rapidly proliferating lymphomas but also one of the most chemosensible tumour diseases. Cures have been reported with one single dose of cyclophosphamid [35]. All our patients achieved CR. In the few cases and small series of adult Burkitt's lymphoma reported in the literature, CR rates vary from 55 to 90% [16, 36–39] but most series included patients with local stage disease whereas our 14 patients all had extensive disease at diagnosis. None of our patients had toxic death. Major toxicity was medullary: 75% of COPADEM modules were followed by a short but severe febrile aplasia requiring hospitalisation. Other treatment modules were much less frequently complicated by severe aplasia and treatment cycles had rarely to be postponed because of medullary toxicity. No cardiac, hepatic or severe renal toxicity were observed. Tumour lysis syndrome occurred in only 1 patient and was easily managed. We think that the good initial tolerance to chemotherapy is due to the low dose COP prephase of this protocol.

6 out of 14 patients relapsed, including 5 within 8 months, as normally seen in Burkitt's lymphoma [12, 41]. 1 patient had a

*Table 3. Relapses after the LMB protocol treatment*

| Patient No. | Initial stage | Protocol | Interval CR/relapse (months) | Localisation of relapse | Outcome |
|---|---|---|---|---|---|
| 1 | III B | LMB84S | 2.5 | Local+distant lymph nodes | CR 15 months after salvage treatment |
| 4 | III B | LMB81 | 2 | Local+CNS | Death 2 months after relapse |
| 5 | III A | LMB84S | 2 | Local | Death 2 weeks after relapse |
| 10 | III B | LMB81 | 3 | BM+CNS | Death 3 months after relapse |
| 11 | III B | LMB84S | 30 | | Second CR 18 months after salvage treatment |
| 13 | III B | LMB84 | 2 | Local+CNS | Death shortly after relapse |

Initial stage: BM, bone marrow; III A, no multiorgan involvements; III B, multiorgan involvement.
Protocol: LMB84S, short arm version; LMB84L, long arm version.
CNS, Central nervous system; BM, bone marrow; CR, complete response.

cytogenetically proven relapse after 30 months. 2 patients could be salvaged by high-dose chemotherapy and autologous (patient No. 1) or allogenic (patient No. 11) BMT. It is now widely accepted that cure rates of 40–50% in relapsing but still chemosensible aggressive lymphomas can be obtained with intensification and BMT, whereas cure rates of 10–20% only are reported with conventional salvage chemotherapy alone [14, 40, 41]. 10 out of 14 (71%) patients are alive and disease-free, 8 out of them with the LMB protocol alone, and 2 of them having required salvage treatment for relapse. These results are comparable to the 65% DFS rate at 29 months with 20 patients including four local stages reported by McMaster *et al.* [36] but seems better when compared with the LNH 84 protocol (35% at 5 years), and Bernstein *et al.* [38] (45% at 3 years) in a comparable group of advanced diseases. We confirm the findings of the paediatric series that initial BM involvement is not an adverse prognostic factor if not associated with CNS involvement [31].

Compared with paediatric patients treated by the same LMB protocol, overall results are less favourable with adult patients, but we conclude that the paediatric LMB protocol is one of the best protocols also for young adults with Burkitt's lymphoma. We have shown this protocol to be feasible mainly in the 16–35 years age group. Our experience is not sufficient to recommend this strategy in older patients. However, the use of haematological growth factors might allow in the future the use of the LMB protocol for older patients also.


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# Phase II Study of Tauromustine in Malignant Glioma

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**46 eligible patients with either anaplastic astrocytoma (AA) or glioblastoma (GBM) and clinical and computed-tomography-confirmed relapse following primary surgery and radiotherapy received oral tauromustine 130 mg/m$^2$ every 5 weeks. A prospective design allowed for concurrent assessment of both clinical and radiological responses and drug toxicity. 41% of patients improved clinically whilst 46% improved radiologically with 3 complete, 7 partial and 7 minimal responses (WHO criteria). Toxicity included grade III or IV gastrointestinal side-effects (15%), grade III or IV leukopenia (24%) and grade III and IV thrombocytopenia (44%). In 9 clinically responding patients, haematological toxicity led to discontinuation of treatment. All patients were followed-up until death and second-line chemotherapy was not used. Median post-treatment survival was 26 weeks for patients with GBM and 57 weeks for patients with AA. Overall 2-year survival rate was 69% for AA and 23% for GBM. Tauromustine given at the time of relapse has demonstrable antitumour activity in patients not previously treated with chemotherapy.**
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## INTRODUCTION

THE PROGNOSIS of patients with malignant glioma (anaplastic astrocytoma, AA; and glioblastoma, GBM) is poor. Despite optimal surgery and high-dose radiation, 80% of patients relapse within 2 years of diagnosis and most of these die shortly thereafter [1–3]. The effectiveness of chemotherapy is limited by tumour chemoresistance and problems with drug delivery [2]. Nitrosoureas are the most commonly used class of drugs and achieve an objective response rate between 30 and 40% [3–6].

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Tauromustine is a nitrosourea based on the endogenous aminoacid taurine. It has demonstrable activity in a number of experimental models [7]. Its toxicity profile is similar to that of other nitrosoureas, with thrombocytopenia as the dose-limiting factor [8, 9]. Therapeutic levels of tauromustine in the brain and brain tumours can be achieved following administration of a single intraoperative dose in patients with malignant gliomas [9]. Here we report a phase II evaluation of tauromustine in patients with AA and GBM who have relapsed following initial surgery and irradiation.

## PATIENTS AND METHODS

Between November 1988 and April 1991 46 patients were entered. The patient characteristics are summarised in Table 1. For entry into the study patients were required to have malignant glioma confirmed by a central review of histopathology using the WHO classification [10]; progressive tumour-related symptoms; computed tomography (CT)-confirmed recurrence; no previous chemotherapy; a minimum of 3 months following completion of high-dose irradiation; WHO performance status 0–2 [11]; and to be clinically stabilised on corticosteroids.