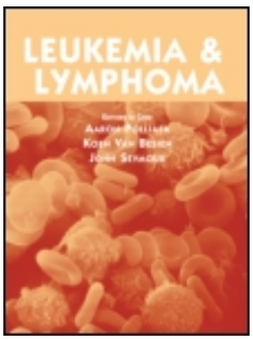

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: https://www.tandfonline.com/loi/ilal20

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To cite this article: A Lacasce, O Howard, S Li, D Fisher, A Weng, D Neuberg & M Shipp (2004) Modified Magrath Regimens for Adults with Burkitt and Burkitt-Like Lymphomas: Preserved Efficacy with Decreased Toxicity, Leukemia & Lymphoma, 45:4, 761-767, DOI: 10.1080/1042819031000141301

To link to this article: https://doi.org/10.1080/1042819031000141301

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Leukemia & Lymphoma, April 2004 Vol. 45 (4), pp. 761–767

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Modified Magrath Regimens for Adults with Burkitt and Burkitt-Like Lymphomas: Preserved Efficacy with Decreased Toxicity

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(Received 14 August 2003)

Burkitt and Burkitt-like lymphomas are rapidly growing tumors which require specialized therapy. Although intensive, multi-agent regimens have been effective in children, results are more variable in adults. Magrath *et al*. previously described a regimen that was highly effective in children and young adults. This phase II study of a modified Magrath regimen was designed to assess its efficacy in older adults and reduce treatment-related toxicity. Fourteen patients with Burkitt/Burkitt-like lymphoma and median age of 47 years were stratified into two categories: low-risk (normal LDH and a single focus of disease measuring less than 10 cm, 3 patients) and high risk (all other, 11 patients). Low-risk patients received three cycles of modified CODOX-M (cyclophosphamide, doxorubicin, adriamycin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate, regimen A). High-risk patients received four alternating cycles of regimens A and B (A-B-A-B). Regimen B consisted of ifosfamide, cytarabine, etoposide and intrathecal methotrexate (IVAC). The modified treatment regimen was associated with no grade 3/4 neuropathy and only one episode of grade 3/4 mucositis. All patients completed protocol therapy and there were no treatment-related deaths. Twelve patients (86%, 90% CI: 61–97%) achieved a complete response; 1 patient achieved a PR and 1 patient died of progressive disease. Nine patients (64%) are alive and disease free at a median follow-up of 29 months. This modified Magrath regimen is effective and well-tolerated in a representative group of older adult patients.

Keywords: Burkitt; Lymphoma; Treatment; Adults

INTRODUCTION

Burkitt and Burkitt-like lymphomas are rapidly growing tumors requiring aggressive therapy [1–3]. In the USA, Burkitt and Burkitt-like lymphomas are unusual in adults, representing less than 5% of all non-Hodgkin's lymphomas (NHL); however, in children, the tumors comprise half of all lymphoid malignancies [1–3].

There are three subtypes of Burkitt lymphoma: endemic, sporadic and immunodeficiency-associated [4]. Endemic Burkitt is found in specific geographic areas in Africa and linked with Epstein Barr virus (EBV) infection whereas sporadic Burkitt occurs in other geographic locations and is less frequently associated with EBV [4]. Among immunocompromised patients, Burkitt lymphomas are primarily seen in association with human immunodeficiency (HIV) infection; only a subset of these tumors are EBV-positive [4].

The distinction between Burkitt and Burkitt-like lymphoma is morphologic [5]. Although both tumor subtypes have a very high mitotic rate and prominent cytoplasmic basophilia with vacuoles, Burkitt lymphomas are characterized by a monomorphic group of intermediate-sized cells with round nuclei and 2 to 5 nucleoli. The tumor cells in Burkitt-like lymphoma are slightly larger with more nuclear variability and increased nucleolar prominence [5].

Burkitt lymphomas exhibit chromosomal translocations which bring c-myc coding sequences under the control of immunoglobulin gene regulatory elements [4]. In Burkitt-like lymphomas, c-myc translocations have been identified with variable frequency [5–7]. Burkitt and Burkitt-like lymphomas express B-cell surface markers

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ISSN 1042-8194 print/ISSN 1029-2403 online © 2004 Taylor & Francis Ltd
DOI: 10.1080/1042819031000141301

including CD19, CD20, surface IgM and CD10 and exhibit high growth fractions when analyzed with cell-cycle specific markers such as Ki67/MIB [4,5].

In the USA, sporadic Burkitt lymphomas commonly present in children and young adults with involvement of the gastrointestinal tract and extranodal disease sites. In contrast, Burkitt-like lymphomas are rare under the age of 18 and typically involve nodal areas with or without extranodal extension.

The initial treatment regimens for Burkitt and Burkitt-like lymphomas were developed in Africa and based on high-dose, single-agent cyclophosphamide [8]. Intrathecal therapy was added later to address the noted high rates of CNS relapse [8]. Based on the success of combination chemotherapy in other lymphoid malignancies, vincristine, doxorubicin, and methotrexate were subsequently added to Burkitt regimens and associated with improved response rates and overall survivals [9]. Later studies demonstrated the superiority of shorter duration, lymphoma-type regimens which included other active agents such as etoposide and cytarabine [10–12]. In children with Burkitt/Burkitt-like lymphomas, such short duration, high intensity regimens have resulted in long-term survival rates of over 80% [12].

Although pediatric intensive multi-agent chemotherapy regimens were also used in adults, the response and survival rates were initially less favorable in older patients [9,13]. However, in 1996, Magrath *et al.* described a modified high-intensity, short-duration regimen that was equally effective in children and adults, including adults with high risk disease [1]. The ''Magrath'' regimen was based on earlier experience with a 15-cycle protocol consisting of cyclophosphamide, doxorubicin, prednisone, vincristine, high-dose methotrexate and intrathecal therapy (CODOX-M) [14]. With CODOX-M, 33 children and 39 adults with Burkitt and Burkitt-like lymphomas had a 56% event-free survival at 2 years [14]. Results were comparable in children and adults, although the average age of the treated adults was only 24 years. Of note, survival was significantly worse for stage IV patients (19%) as compared with stage I–III patients (66%).

In a follow-up protocol, Magrath *et al.* decreased the number of cycles of CODOX-M therapy (COXOX-M) in low-risk patients and added a second alternating 4-course therapy for high-risk patients [1]. Low-risk patients—defined as having a single focus of disease less than 10 cm in maximal diameter and a normal LDH—received 3 courses of CODOX-M (regimen A, A-A-A). High-risk patients—all others—received 4 (total) courses of regimen A alternating with a second regimen (B) containing ifosfamide, etoposide and high-dose cytarafine (IVAC) (A-B-A-B) [1]. In both low- and high-risk patients, therapy lasted no longer than 4 months.

Twenty-one children and 20 adults were treated with the indicated low- and high-risk regimens, although the median age of adult patients was only 25 years [1]. The event-free survival of all patients at 2 years was 92%; results were again comparable in adults and children. Of additional interest, low-risk patients treated with three cycles of regimen A and high-risk patients treated with 4 cycles of alternating A and B regimens did equally well [1]. Although this treatment was effective in young adults, it was not clear that the regimen could be given or be as effective in older patients. This was particularly important because the treatment was associated with significant neurologic toxicity, myelosuppression and mucositis in younger patients.

For these reasons, we designed a phase II, prospective study of a modified Magrath regimen in adults with Burkitt and Burkitt-like lymphomas. Modifications to regimen A (CODOX-M) of the previously reported Magrath regimen include [1]: (1) decreasing cyclophosphamide dose to reduce myelosuppression; (2) capping vincristine dose and reducing intrathecal cytarabine dose to limit neurotoxicity; (3) decreasing intravenous methotrexate dose to reduce toxicity while maintaining adequate CNS penetration; and (4) moderately increasing doxorubicin dose to preserve regimen intensity. In this study, our primary objectives were to reduce the toxicity of the original protocol and evaluate the efficacy of the modified regimen in a representative group of older adult patients.

MATERIALS AND METHODS

Patients

Patients with newly diagnosed Burkitt and Burkitt-like lymphomas underwent complete staging with CT scans of the chest, abdomen, and pelvis, gallium scan, bone marrow biopsy and cerebral spinal fluid sampling. Eligibility criteria were as follows: age greater than 18 and less than 65, histologically confirmed Burkitt and Burkitt-like lymphomas, measurable or evaluable disease (defined as reproducibly measurable disease in two perpendicular dimensions on radiologic study or the presence of disease on bone marrow biopsy), absolute neutrophil count $> 1{,}500$ and platelets $> 100{,}000$, adequate renal and hepatic function, cardiac ejection fraction of $> 50\%$ and HIV-negative status. Exclusion criteria included: previous therapy with chemotherapy or radiation, uncontrolled infection, significant co-morbid pulmonary or cardiac disease, pregnancy, concomitant malignancy (except basal cell carcinoma of the skin and *in situ* carcinoma of the cervix), and major surgery within 2 weeks.

Diagnostic tumor biopsies from all 14 study patients were reviewed by a single hematopathologist (A.W.) and classified as Burkitt or Burkitt-like according to the Revised European American Lymphoma classification criteria. Briefly, these tumors were diffuse in architecture and comprised of a monotonous population of intermediate-sized cells showing only modest variation in size and shape. The nuclei of these cells were generally round to oval in shape with coarse chromatin, multiple small distinct nucleoli (occasional cells with single prominent

nucleoli were accepted), and scant to limited amounts of amphophilic cytoplasm. These tumors also showed high mitotic rates and were interspersed with tingible body macrophages which imparted a "starry-sky" appearance at low-power examination. All tumors were considered to be distinct from diffuse large B-cell lymphoma based on morphologic criteria. In 12 patients, tumor MIB fraction was formally evaluated; diagnostic fine-needle aspirates were insufficient for MIB staining in the other 2 patients. Ten of the 12 evaluable patients had MIB fractions of 90% or greater; the 2 patients with MIB fractions less than 90% had a t(8;14) and a complex karyotype involving chromosome 14, respectively.

Patients were staged according to Murphy criteria: (1) Stage I, a single focus of disease, nodal or extra-nodal, excluding the abdomen and mediastinum; (2) Stage II, a single extranodal tumor with regional nodal involvement, primary gastrointestinal tumor with or without mesenteric lymph node involvement, two or more nodal areas on the same side of the diaphragm, or two single tumors with or without regional node involvement; (3) Stage III, two single, extranodal sites on both sides of the diaphragm, two or more nodal areas on both sides of the diaphragm; all primary intrathoracic tumors, all extensive intra-abdominal disease and all primary paraspinal or epidural tumors regardless of other sites involved; (4) Stage IV, any of the above with initial central nervous system involvement or bone marrow involvement [15].

Patients were stratified into 2 risk groups based on previously described criteria [1]. Low-risk patients had a normal LDH and a single focus of disease measuring less than 10 cm in greatest diameter; all others were considered high risk. The protocol and the consent form were approved by the Institutional Review Board and all study patients gave written, informed consent.

Treatment Regimen

The modified Magrath regimen is shown in Fig. 1. As previously described, all low-risk patients received 3 cycles of regimen A (CODOX-M). High-risk patients received alternating cycles of regimens A and B (IVAC) for a total of 4 cycles (A-B-A-B). G-CSF support was used with all cycles.

Several modifications were made to regimen A (CODOX-M) of the previously reported Magrath regimen [1] (Fig. 1). Cyclophosphamide was changed from 800 mg/m^2 day 1 followed by 200 mg/m^2 days 2–5 to 800 mg/m^2 days 1 and 2 to reduce myelosuppression. Vincristine was capped at 2 mg total and the dose of intrathecal cytarabine was reduced from 70 mg to 50 mg to reduce the incidence of neurotoxicity. The systemic dose of intravenous methotrexate was decreased from 6,720 mg/m^2 to 3,000 mg/m^2 to reduce toxicity while maintaining adequate CNS penetration. Doxorubin dosing was increased from 40 mg/m^2 to 50 mg/m^2.

Regimen A consisted of cytoxan 800 mg/m^2 days 1 and 2, adriamycin 50 mg/m^2 day 1 and vincristine 1.4 mg/m^2 (2 mg maximum dose) on day 1. Twelve mg of intrathecal methotrexate mixed with 50 mg of cytarabine was given day 1, and 50 mg of intrathecal cytarabine was given day 3. All intrathecal therapy was mixed with 50 mg hydocortisone. G-CSF was given days 3 through 8. On day 10, patients received vincristine 1.4 mg/m^2 (2 mg maximum dose) and methotrexate 3 grams/m^2 after alkalinization of the urine (pH < 7). Twenty-four hours later, leucovorin was initiated with a dose of 200 mg/m^2 followed by 15 mg/m^2 every 6 h until the methotrexate level was less than $0.1 \times 10 - 6$ M. G-CSF was restarted thereafter if ANC > 1000.

Regimen B was initiated once counts had recovered following cycle A. Treatment consisted of cytarabine 2,000 mg/m^2 q 12 h for 4 doses with decadron eye drops, etoposide 60 mg/m^2 daily for 5 days, and ifosfamide 1,500 mg/m^2 qd for 5 days with equal-dose mesna in divided doses. Twelve mg of intrathecal methotrexate was administered on day 5. G-CSF was started on day 6 and continued until neutropenia resolved.

Patients with central nervous system involvement at diagnosis received additional doses of intrathecal therapy during cycle 1 of both the A and B regimen as follows: A cycle—50 mg of cytarabine on day 5 and 12 mg of methotrexate 12 mg on day 10; B cycle—50 mg of cytarabine day 3 and 50 mg cytarabine with 12 mg methotrexate day 5.

Response and Toxicity

Complete response (CR) was defined as disappearance of all symptoms and signs of measurable or evaluable disease for greater than 4 weeks off therapy. Complete Response with Residual Abnormality (CR_{RA}) was defined as CR except for a persistent gallium-negative mass in the mediastinum or abdomen which regressed more than 50% after the first 3 cycles of chemotherapy with no further change on subsequent treatment. Partial response was defined as a reduction of 50% or greater in the sum of the products of the perpendicular diameters of all measurable disease lasting more than 4 weeks.

Toxicity was graded on a scale of 0 to 5 by the National Cancer Institute Common Toxicity Criteria version 2.0.

Statistical Methods

Progression-free survival (PFS) was measured from date of initial diagnosis to date of progression or death in absence of progression. Patients in continued remission were censored on their last date of follow-up. Overall survival (OS) was defined as duration of time between initial diagnosis and death or last known follow-up. Two-year OS and PFS were calculated using the Kaplan-Meier method and confidence intervals (CI) were determined using Greenwood's formula [16,17]. Ninety percent confidence intervals were computed using the exact binomial calculation.

Regimen A: CODOX-M

Day	1	2	3	4	5	6	7	8	9	10	11	12	13
Cyclophosphamide 800 mg/m^2	x	x											
Vincristine[b] 1.4 mg/m^2	x									x			
Doxorubicin 50 mg/m^2	x												
Methotrexate 3gm/m^2										x			
Leucovorin											x		
IT Cytarabine 50mg	x												
IT Methotrexate 12 mg	x												
IT Cytarabine 50mg			x[c]										
G-CSF[d]	x	x	x	x	x	x						x	x

Regimen B: IVAC

Day	1	2	3	4	5	6	7	8	9	10	11	12	13
Ifosfamide 1500 mg/m^2	x	x	x	x	x								
Mesna	x	x	x	x	x								
Etoposide 60 mg/m^2	x	x	x	x	x								
Cytarabine 2gm/m^2[e]	x	x	x	x									
IT Methotrexate12 mg					x								
G-CSF						x	x	x	x	x	x	x	x

[a] Low-risk patients receive 3 cycles of regimen A (A-A-A). High-risk patients receive 4 alternating cycles of regimens A and B (A-B-A-B).

[b] Vincristine maximum 2mg dose.

[c] High-risk only.

[d] ANC < 1000 on day 12, restart G-CSF.

[e] Cytarabine 2g/m^2 q12hr x 4 doses.

Changes from original Magrath regimen (all in regimen A):

Change Cyclophosphamide from 800mg/m^2 d1 and 200mg/m^2 d2-5 to 800mg/m^2 d1 and 2 only

Cap Vincristine at 2mg total dose

Increase Doxorubicin from 40mg/m^2 to 50mg/m^2

Decrease IV Methotrexate from 6.7 gm/m^2 to 3 gm/m^2

Decrease IT Cytarabine from 70mg to 50m

FIGURE 1 All low-risk patients received 3 cycles of regimen A (CODOX-M). High-risk patients received alternating cycles of regimen A and B (IVAC) for a total of 4 cycles (A-B-A-B). G-CSF support was used with all cycles. Several modifications were made to regimen A (CODOX-M) of the previously reported Magrath regimen. Cyclophosphamide was changed from 800 mg/m^2 day 1 followed by 200 mg/m^2 days 2–5 to 800 mg/m^2 days 1 and 2 to reduce myelosuppression. Vincristine was capped at 2 mg total and the dose of intrathecal cytarabine was reduced from 70 mg to 50 mg to reduce the incidence of neurotoxicity. The systemic dose of intravenous methotrexate was decreased from 6,720 mg/m^2 to 3,000 mg/m^2 to reduce toxicity while maintaining adequate CNS penetration. Doxorubin dose was increased from 40 mg/m^2 to 50 mg/m^2.

RESULTS

Patient Characteristics

The clinical characteristics of the 14 adult study patients are shown in Table I. In this representative adult population, the median age was 47 years (range 18–65). Three patients had low-risk disease and 11 had high-risk disease. Thirty-five percent of patients presented with Murphy stage I or II disease, whereas 65% had stage III or IV disease. No patients had cytologically proven CNS involvement at presentation; however, 5 patients had bone marrow involvement, ranging from 25% (1 patient) to greater than 70% (4 patients).

Toxicity

Using the modified regimen, there were no therapy-related deaths and all patients completed protocol therapy. There were no cases of grade 3 or 4 peripheral neuropathy and only one episode of grade 3/4 mucositis.

The observed hematologic toxicities included grade 3 or 4 leukopenia and thrombocytopenia in 100% of the B cycles (Table II). Seventy-four percent of A cycles were

TABLE I Patient characteristics

Age:	
Median	47
Range	18–65
Risk:	
Low	3
High	11
Disease Description (Murphy)	
Stage I	4 (28%)
Stage II	1 (7%)
Stage III	4 (28%)
Stage IV	5 (36%)
Bone marrow involvement	5 (36%)

TABLE II Treatment-related toxicity

Toxicity	Regimen	Grade 3 or 4 Toxicity (% cycles)
Neutropenia	A	74%
	B	100%
Thrombocytopenia	A	36%
	B	100%
Febrile Neutropenia	A	17%
	B	43%

complicated by grade 3 or 4 leukopenia and 36% of A cycles were associated with grade 3 or 4 thrombocytopenia (Table II). Febrile neutropenia occurred in the setting of grade 3/4 neutropenia in 17% of A and 43% of B treatment cycles, respectively (Table II).

Other grade 3 or 4 toxicities included one episode each of catheter infection, supraventricular tachycardia, pulmonary infiltrate, and two episodes of catheter-related thrombosis.

Response to Therapy and Survival

Eighty-six percent (90% CI: 61–97%) of all patients, including all 3 low-risk patients and 9 of 11 high-risk patients, achieved a CR or CR_{RA} with this treatment (Table III). The remaining 2 patients, who both had high-risk disease, achieved only a transient PR or no response to therapy; both of these patients subsequently died of progressive disease (Table III). Of the 12 complete responders, 9 remain in CR with a median follow-up of 29 months. Three patients relapsed from CR; all 3 patients underwent subsequent high dose therapy with stem cell transplant with 1 patient in continued second CR (Table III).

At 2 years, PFS for all patients was 64% (90% CI: 43–85%) and OS for all patients was 71% (90% CI: 50–91%) (Fig. 2A,B). In high-risk patients, PFS and OS were 60% (90% CI: 85%) and 60% (90% CI: 35–85%), respectively (Fig. 2C,D).

TABLE III Response to therapy

Response:	# Patients
CR/CR_{RA}	12 (86%, 90% CI 61–97%)*
PR	1**
Progressive disease	1**

*Nine patients obtained durable CRs and 3 patients relapsed from CR. All 3 relapsed patients underwent subsequent high-dose therapy with stem cell rescue; 1 patient remains in continued CR; 1 died of progressive disease and 1 died of treatment-related toxicity.
**Died of progressive disease.

DISCUSSION

Our data indicate that a modified Magrath regimen is effective and well tolerated in a representative group of adult patients with Burkitts or Burkitt-like lymphoma. Eighty-six percent of patients achieved a complete response to therapy and 64% of patients are alive and disease-free at a median follow-up of 29 months. Patients with low-risk disease did particularly well with 100% survival. These encouraging results were achieved with a modified treatment schema, in which the doses of intrathecal cytarabine and systemic methotrexate and vincristine were decreased and the cyclophosphamide administration was altered. With these modifications, several of the most severe treatment-related toxicities were markedly reduced.

Our results compare favorably to those obtained with the original regimen in younger patients. The initial report of the original regimen included 20 adults with a median age of 25 years; all achieved a CR to therapy and remained disease free with median follow-up of 32 months [1]. However, the highly effective regimen was associated with severe neurotoxicity, with 27% of patients experiencing severe neuropathy and motor weakness and 2 patients suffering seizures. A possible association with concurrent GM-CSF administration was suggested. In the original study, there was also a high (58%) incidence of severe (grade 3/4) mucositis.

In a recently reported follow-up study, the United Kingdom Lymphoma Group evaluated the efficacy of CODOX-M/IVAC in 52 adult patients with Burkitt's lymphoma and a median age of 35 [18]. Their treatment protocol was similar to the original Magrath regimen, with the exception of capped vincristine doses at 2 mg and G-CSF, rather than GM-CSF, support. Two-year PFS and OS were 65% and 73%, respectively. In contrast to the initial CODOX-M/IVAC trial, neurotoxicity in the follow-up study was mild with a single patient developing grade III neuropathy. However, overall treatment-related toxicity was severe. Twenty-one percent of patients were unable to complete therapy and only 43% of high-risk patients received full-dose therapy. There were also 3 treatment-related deaths.

Our results extend those of the United Kingdom Lymphoma group, demonstrating that a modified Magrath regimen is also effective in much older patients

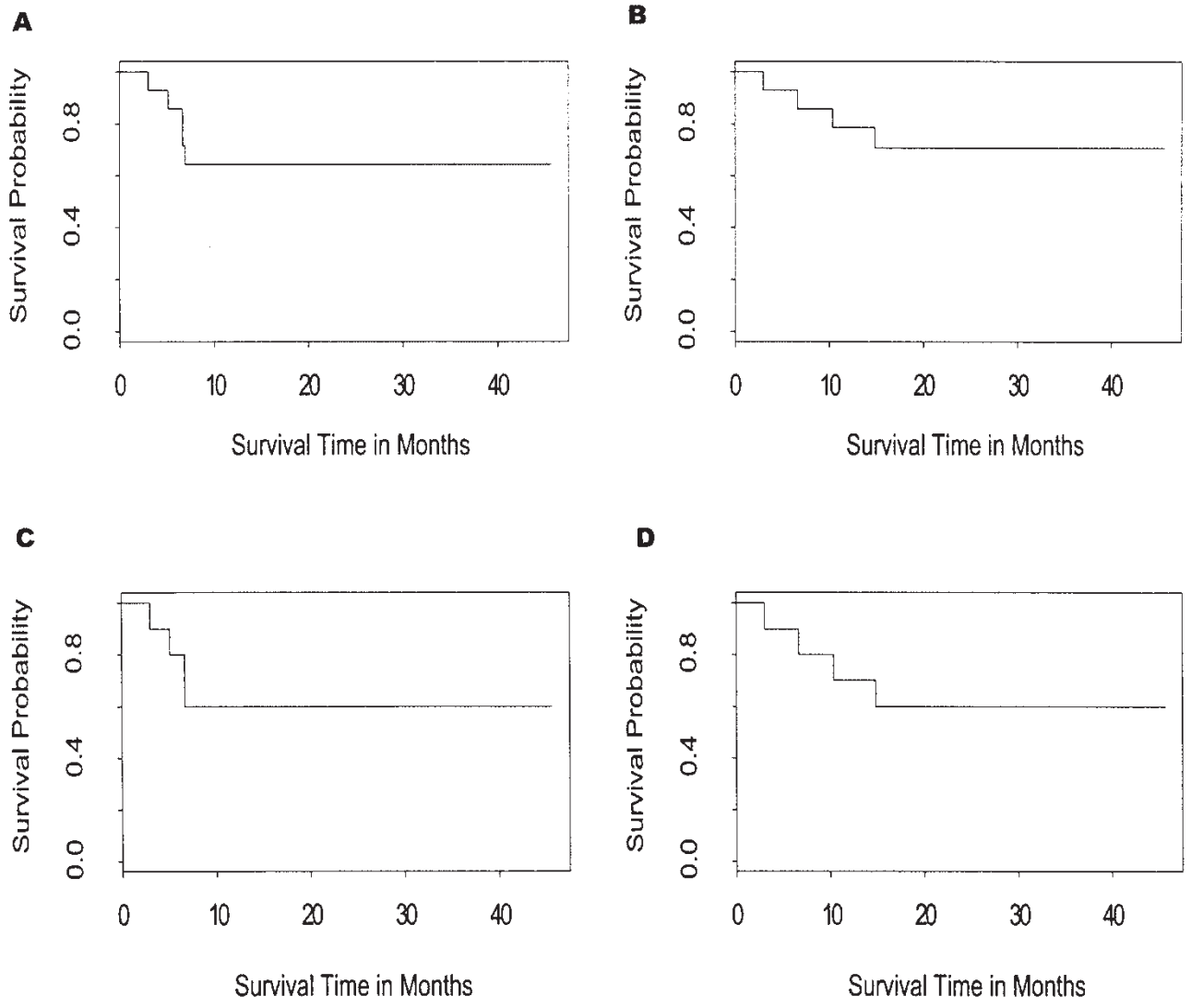

FIGURE 2 Progression-free and overall survival for patients treated with the modified Magrath regimen. (A and B) PFS and OS for all patients. (C and D) PFS and OS for high-risk patients.

(median age 47 [this study] vs. 35 years [UKLG, [18]] vs. 25 years [initial trial, [1]]). Our data also suggest that the dose and schedule modifications to this intensive multi-drug regimen dramatically reduce treatment-related toxicities, with all patients completing therapy and no treatment-related deaths.

In a recent Cancer and Leukemia Group B study, 30 patients with Burkitt or Burkitt-like lymphoma and a median age of 44 years were treated with a multi-agent regimen and cranial irradiation for an extended time period [2]. Eighty-three percent of patients achieved CR and 57% were alive at a median follow-up of 5.1 years [2]. All relapses occurred prior to 16 months following the completion of therapy. Although the efficacy of the modified Magrath regimen and the more prolonged therapy were comparable, the prolonged treatment was considerably more toxic, with 4 treatment-related deaths. Neurologic complications were severe, including transverse myelitis, severe peripheral neuropathy, transient aphasia and cortical blindness which prompted the removal of cranial irradiation from the protocol. Hematologic and infectious complications were also very common and fewer than 60% of patients received all seven cycles of chemotherapy [2].

Taken together, these studies indicate that the modified Magrath regimen preserves efficacy in a representative adult patient group while reducing the severe toxicities of the original therapy or similar more prolonged treatment regimens. For this reason, our future studies in these diseases will be based on this effective and well-tolerated regimen.

Acknowledgements

Ann LaCasce is a fellow in the Clinical Investigator Training Program, Harvard IMIT Health Sciences and Technology, Beth Israel Deaconess Medical Center in collaboration with Pfizer.

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