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A dose-dense short-term therapy for human immunodeficiency virus/acquired immunodeficiency syndrome patients with high-risk Burkitt lymphoma or high-grade B-cell lymphoma: safety and efficacy results of the "CARMEN" phase II trial

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Summary

A few prospective trials in HIV-positive patients with Burkitt lymphoma (BL) or high-grade B-cell lymphoma (HGBL) have been reported. Investigated therapies have shown good efficacy but relevant safety problems, with high rates of interruptions, severe mucositis, septic complications, and fungal infections. Here, we report the results of a multicentre phase II trial addressing a new dose-dense, short-term therapy aimed at maintaining efficacy and improving tolerability. The experimental programme included a 36-day polychemotherapy induction followed by high-dose cytarabine-based consolidation and response-tailored BEAM (carmustine, etoposide, cyatarabine, and melphalan)- conditioned autologous stem cell transplantation (ASCT). This therapy would be considered active if ≥11 complete remissions (CR) after induction (primary endpoint) were recorded among 20 assessable patients. HIV-positive adults (median age 42, range 26–58; 16 males) with untreated BL (n = 16), HGBL (n = 3) or double-hit lymphoma (n = 1) were enrolled. All patients had high-risk features, with meningeal and bone marrow infiltration in five and nine patients respectively. The experimental programme was safe and active in a multicentre setting, with only two episodes of grade 4 non-haematological toxicity (hepatotoxicity and mucositis), and no cases of systemic fungal infections; two patients died of toxicity (bacterial infections). Response after induction (median duration: 47 days; interquartile range 41–54), was complete in 13 patients and partial in five [overall response rate = 90%; 95% confidence interval (CI) = 77–100]. All responders received consolidation, and five required autologous stem cell transplant. At a median follow-up of 55 (41–89) months, 14 patients are relapse-free and 15 are alive, with a five-year progression-free survival and an overall survival of 70% (95% CI = 60–80%) and 75% (95% CI = 66–84) respectively. No patient with cerebrospinal fluid (CSF)/meningeal lymphoma experienced central nervous system recurrence. With respect to previously reported regimens, this programme was delivered in a shorter period, and achieved the main goal of maintaining efficacy and improving tolerability.

Keywords: Human Immunodeficiency Virus, Burkitt lymphoma, high-grade B-cell lymphoma, double-hit lymphoma, *MYC*, central nervous system prophylaxis.

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Treatment of HIV/AIDS patients with Burkitt lymphoma (BL) or high-grade B-cell lymphoma (HGBL) is a hard challenge, requiring multidisciplinary efforts and demanding strategies. While the worldwide use of highly active antiretroviral therapy (HAART) resulted in improved tolerability and efficacy of standard chemotherapy in HIV-positive patients with diffuse large B-cell lymphomas, it has not been associated with better outcome in HIV/AIDS patients with BL, with respect to the pre-HAART era, suggesting that more intensive treatments should be used.[12] Current worldwide experience with chemotherapy in HIV/AIDS patients with BL and other *MYC*-translocated aggressive lymphomas is still limited. In the rituximab era, only three prospective trials, addressing modified GMALL, CODOX-M/IVAC or DA-EPOCH regimens, have been reported.[17,14,8] Investigated regimens display high efficacy, with a two-year overall survival (OS) ~70%, but are delivered in 126–168 days, and show important dose-limiting side effects, prolonged hospitalisation and a treatment-related mortality of up to 16%. Moreover, one third of patients did not complete treatment, often due to toxicity, such as severe mucositis, septic complications and fungal infections. Literature on the management of HIV/AIDS patients with HGBL is limited to a few cases, usually analysed together with patients with BL, and sometimes a central pathology review was not performed. The term HGBL was defined by the WHO 2017 classification,[11] and replaces the 2008 category of 'unclassifiable B-cell lymphoma with features intermediate between diffuse large B-cell lymphoma and BL'.[22] A new category called HGBL with *MYC* and *BCL-2* and/or *BCL-6* translocations has been established in the last WHO classification, which regards the cases of 'double-/triple-hit' lymphomas, whereas follicular, transformed or lymphoblastic lymphomas with these chromosomal abnormalities are classified separately.

A dose-dense, short-term chemotherapy programme including seven active drugs and intrathecal drug delivery has shown excellent activity and safety profiles in HIV-negative patients with BL in the prerituximab era.[7] We introduced a few changes to this regimen to use it with maintained efficacy and improved tolerability in HIV/AIDS patients with BL. In particular, six doses of rituximab were added and methotrexate dose was reduced from 150 and 250 mg/kg to 3 g/m^2, mostly to avoid mucositis, which constitutes an important route of access for infectious agents and is one of the main causes of death in these patients.[10] A pilot retrospective experience suggested that this combination is safe and effective in HIV/AIDS patients with BL, with no cases of grade 4 mucositis and opportunistic infections, a complete remission rate (CRR) of 80%, and a two-year OS of 73%.[9]

On these notions, we addressed efficacy and tolerability of this dose-dense, short-term programme in HIV/AIDS patients with BL or HGBL in a multicentre phase II trial called 'CARMEN'. After a long observation period, this simple and cost-beneficial therapy showed excellent safety and efficacy profiles, which leads us to suggest the use of this new combination in HIV/AIDS patients with BL or HGBL and to investigate this strategy in other aggressive lymphomas.

Patients and methods

Trial design and study group

The CARMEN study was a multicentre, single-arm phase II trial addressing feasibility and activity of a new dose-dense sequential chemoimmunotherapy in HIV/AIDS patients with untreated BL or HGBL. Selection criteria were: (i) histologically-proven diagnosis of BL or of 'unclassifiable B-cell lymphoma with features intermediate between DLBCL and Burkitt lymphoma' according to the WHO 2008 classification;[22] (ii) HIV seropositivity; (iii) no previous treatment for lymphoma; (iv) age 18–60 years; and (v) Eastern Cooperative Oncology Group (ECOG) performance status score $\leq$3. Patients with brain lesions were excluded, whereas patients with meningeal disease were considered. Patients with prior organ transplant or other malignancies were excluded. Hepatitis B (HBV) or C (HCV) virus infections did not constitute exclusion criteria. Diagnostic histopathological material of registered cases was reviewed by expert haematopathologists (F.F. and M.P.), fluorescence *in-situ* hybridisation (FISH) for *MYC*, *BCL-2* and *BCL-6* was performed centralised and lymphoma entities re-classified according to the WHO 2017 classification.[11] Written informed consent was obtained from each patient once eligibility was confirmed and after patient's review of the protocol contents. This trial conformed to the Declaration of Helsinki and was approved by the Institutional Review Boards (IRBs) of the participating institutions. Staging work-up and pretreatment tests were performed within 14 days before the start of treatment and are listed in Table I.

Experimental treatment

The experimental therapeutic programme is reported in Fig 1. It consisted of a 36-day induction course of sequential doses of fractionated cyclophosphamide, vincristine, rituximab, methotrexate, etoposide, and doxorubicin, plus conventional triple-drug intrathecal chemotherapy delivered every 14 days (Table I, see footnote for details). In the case of meningeal involvement, intrathecal therapy consisted of six weekly doses. Liposomal cytarabine 50 mg as alternative to the conventional triple-drug scheme was permitted.

Subsequent treatment was tailored according to the objective tumour response to the induction phase (Fig 1): patients in complete remission (CR) received high-dose-cytarabine-based consolidation (Table 1), patients in partial response (PR) received consolidation plus BEAM (carmustine, etoposide, cytarabine, and melphalan)/FEAM (fotemustine,

Table I. Induction and consolidation phases.

Day	Drug/dose/administration schedule
Induction	
−2	Methylprednisolone 0·5–1 mg/kg/d i.v.
−1	Methylprednisolone 0·5–1 mg/kg/d i.v.
0	Methylprednisolone 0·5–1 mg/kg/d i.v.
	Cyclophosphamide 500 mg/m^2 over 1 h infusion
	Vincristine 2 mg total dose i.v. bolus
1	Methylprednisolone 0·5–1 mg/kg/d i.v.
	Cyclophosphamide 500 mg/m^2 over 1 h infusion
2	Rituximab 375 mg/m^2
5	Methotrexate 12 mg + cytarabine 50 mg + steroids by i.t. route
7	Methotrexate 3 g/m^2 i.v. over 6 h with leucovorin rescue therapy*
14	Rituximab 375 mg/m^2
15	Etoposide 250 mg/m^2 every 12 h
19	Methotrexate 12 mg + cytarabine 50 mg + steroids by i.t. route
21	Methotrexate 3 g/m^2 i.v. over 6 h with leucovorin rescue therapy*
29	Rituximab 375 mg/m^2
	Doxorubicin 50 mg/m^2 i.v. bolus
33	Methotrexate 12 mg + cytarabine 50 mg + steroids by i.t. route
36	Rituximab 375 mg/m^2
	Vincristine 2 mg total dose i.v. bolus
Consolidation†	
50–51	Cytarabine 2 g/m^2 in a 3-h infusion, twice a day (every 12 h)
52	Rituximab 375 mg/m^2
60	Rituximab 375 mg/m^2

i.v., intravenous route; i.t., intrathecal route.

*Intravenous alkalinization was used to promote excretion of methotrexate according to institutional guidelines. Calcium leucovorin was administered at a dose of 15 mg/m^2 i.v. starting 24 h after completing methotrexate infusion, and continued every 6 h for 12 doses or, in excess, until methotrexate blood levels were less than 0·2 μmol/l. Methotrexate serum levels were monitored at 48, 72 and 96 h from methotrexate infusion and leucovorin dose was adjusted according to methotrexate serum levels. Staging work-up included physical examination, contrast-enhanced total-body computed tomography (CT) scan, 18-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET), gadolinium-enhanced whole-brain magnetic resonance imaging (MRI), bone marrow biopsy and aspirate, and cerebrospinal fluid examination (cell count, physic-chemical exams, cytological examination, flow cytometry). Pretreatment tests were Eastern Cooperative Oncology Group (ECOG) score definition, biochemical serum profile, CD4/CD8 T-cell quantification, human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) serological evaluation, HIV-RNA viral load, HIV resistance testing, cytomegalovirus (CMV), Epstein–Barr virus (EBV) and *Toxoplasma* IgG and IgM, human herpesvirus (HHV)-6–8 and parvovirus markers, echocardiography, respiratory volumes assessment, and pregnancy test.

†Leukapheresis to collect autologous peripheral-blood stem cells was performed after consolidation, starting granulocyte colony-stimulating factor 24 h after the last dose of cytarabine. Dose intensity was maintained using granulocyte colony-stimulating factor whenever neutrophil count was $\leq 1{\cdot}5 \times 10^9$/l. Antimicrobial prophylaxis (acyclovir 400 mg twice/day, fluconazole 200 mg once a day and trimethoprim 160 mg/sulphamethoxazole 800 mg three times/week) was used. Levofloxacin 500 mg/day was added in patients with grade 4 neutropenia.

etoposide, cytarabine, and melphalan)-conditioned autologous stem cell transplantation (ASCT; Table II), patients with stable or progressive disease received high-dose sequential intensification (Table II). Involved-field irradiation (36 Gy) was permitted according to institutional guidelines in patients with initial bulky disease or a single positron emission tomography (PET)-positive residual lesion.

Duration of induction (days) was estimated from the first to the last day of drug delivery of the induction course. Duration of the whole programme (days) was estimated from the first day of the induction course to the last day of drug delivery of the consolidation. For patients who received ASCT, the duration of the whole programme was estimated from the first day of the induction course to the date of autologous stem cell reinfusion; duration data are expressed in median and interquartile range (IQR).

Toxicity and response assessment

Treatment side effects were assessed separately for each chemotherapy phase, and graded according to the NCI-NCIC CTC version 3.0.[23] The worst toxicity per organ was considered per patient. Response was assessed after induction, after consolidation and at the end of the whole programme by whole-body computed tomography (CT) scan, 18-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) and other exams that were positive at baseline. Response definition followed the Revised Response Criteria for Malignant

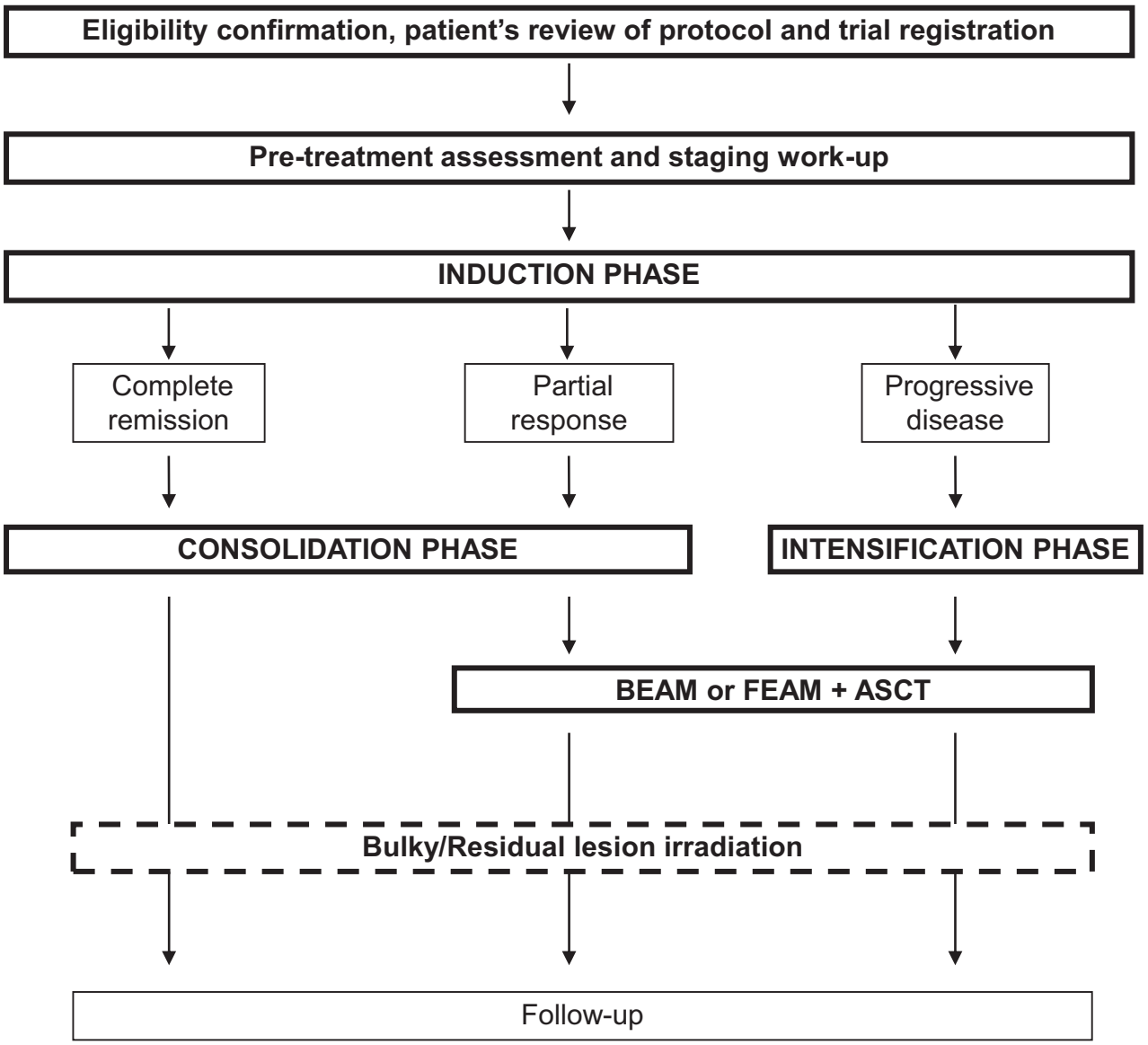

Fig 1. Therapeutic program. CR, complete remission; PR, partial response; SD, stable disease; PD, progressive disease; TD, toxic death; RT, radiotherapy; BEAM, carmustine, etoposide, cytarabine, and melphalan; FEAM, fotemustine, etoposide, cytarabine, and melphalan; ASCT, autologous stem cell transplant. Chemotherapy details are reported in Tables I and II.

Lymphoma.[4] In cases with concomitant positive cerebrospinal fluid (CSF), cytology examination was performed before every intrathecal chemotherapy dose, a reduction of >50% of cell number was considered PR, while a lower reduction was considered stable disease. Radiograms regarding response assessment were not centrally reviewed. After end of treatment, the disease was assessed every three months for the first two years, every six months during the third, fourth and fifth years and every year thereafter.

Statistical considerations

The primary endpoint was CRR after induction chemoimmunotherapy. CRR according to investigator assessment was used as supportive evidence. The two-stage Simon optimal design was used to test the null hypothesis that the true CRR after the induction phase is 40% (considered unacceptable) as opposed to the alternative hypothesis of 70% (considered of interest). With a type I error of 5% and a power of 80%, three CRs or more after the induction phase were required among the first seven patients to proceed to the second stage whereby an additional 13 patients would be enrolled (total: 20 patients). If ≥11 CRs were achieved, this regimen would be declared active in this setting.

Toxicity, activity of the whole programme, progression-free survival (PFS), and OS were the secondary end-points. Survival curves were generated using the Kaplan–Meier method. PFS and OS were estimated according to Revised

Table II. Intensification phase and myeloablative chemotherapy

	Drug/dose/administration schedule
Intensification	
Weeks 1 & 4	One or two courses of R-IVAC or R-ICE (debulking chemotherapy)
Weeks 7–8	Cyclophosphamide 4 g/m^2
	Rituximab 375 mg/m^2 on days 3 and 10
	In vivo purged PBPC collection (day 11–13)
Weeks 11–12	Cytarabine 2 g/m^2 every 12 h for four days (days −5 to −2)
	Rituximab 375 mg/m^2 (day −1 and +11)
	Second *in vivo* purged PBPC collection (only if needed)
BEAM regimen	
Day 1	Carmustine* 300 mg/m^2
Days 2–5	Etoposide 100 mg/m^2 every 12 h
	Cytarabine 200 mg/m^2 every 12 h
Day 6	Melphalan 140 mg/m^2
Day 8	Reinfusion of ≥5 × 10^6 CD34+ cells/kg body weight

R-IVAC, rituximab, ifosfamide, etoposide, cytarabine, cyclophosphamide; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; PBPC, peripheral blood progenitor cells.
*When it was not available, carmustine was replaced by fotemustine 150 mg/m^2/day on days 1 and 2 (FEAM regimen).

Response Criteria for Malignant Lymphoma.[4] All analyses were carried out using the Statistica 10.0 statistical package for Windows (Statsoft Inc, 2011, Tulsa, OK, USA). This study is registered with ClinicalTrials.gov number NCT01516593 (CARMEN trial).

Results

Study population

Twenty patients (median age 42, range 26–58; 16 males) were recruited at seven centres between May 2012 and December 2015. The trial was ended after accrual completion, and the database lock for the primary analysis was August 1, 2019. After central pathology review, 16 patients had a BL, three patients had a HGBL not otherwise specified and one had a HGBL with *MYC* and *BCL-6* translocations (double-hit lymphoma). All patients had high-risk disease according to the British Columbia Cancer Agency (BCCA) risk score and 19 (95%) had high-risk according to the Magrath score, with an age-adjusted international prognostic index (IPI) score ≥2 in 19 (95%) patients (Table III). Five (25%) patients had CSF/meningeal disease, nine (45%) had bone marrow infiltration, and three (15%) had leukaemic disease. At baseline, whole-body CT scan and ^{18}FDG-PET were positive in all the enrolled patients, and additional positive exams were bone marrow biopsy (n = 9), CSF exams (n = 5), testes ultrasonography (n = 2), gastroscopy (n = 3), colonoscopy

Table III. Patient characteristics.

Variable	No. (%)
No. of patients	20
Median age (range)	42 (26–58)
Male	16 (80%)
Stage III–IV	20 (100%)
High risk according to BCCA score*	20 (100%)
High risk according to Magrath score†	19 (95%)
Age-adjusted IPI score ≥2	19 (95%)
ECOG Performance status >1	7 (35%)
Increased lactate dehydrogenase serum level	15 (75%)
B symptoms	12 (60%)
CNS involvement‡	5 (25%)
Bone Marrow infiltration	9 (45%)
Extranodal disease	18 (90%)
Bulky disease	6 (30%)
Lymphoma entity	
Burkitt lymphoma	16 (80%)
High-grade B-cell lymphoma not otherwise specified	3 (15%)
Double-hit lymphoma	1 (5%)
Hepatitis C virus seropositivity	2 (10%)
HbsAg$^+$/HbcAb$^+$	6 (30%)
Median CD4$^+$ count (range) [cells/μl]	327 (1–560)
CD4$^+$ count <200 cells/μl	4 (20%)
Median HIV-RNA (range) [copies/ml]	0 (0–1044652)
HIV-RNA <50 copies/ml	12 (60%)
HAART before lymphoma diagnosis§	13 (65%)
HAART since lymphoma diagnosis¶	7 (35%)
HAART	
Emtricitabine/tenofovir + ritonavir + atazanavir	2 (10%)
Emtricitabine/tenofovir + ritonavir + darunavir	4 (20%)
Emtricitabine/tenofovir + ritonavir + lopinavir	1 (5%)
Emtricitabine/tenofovir + ritonavir + atazanavir + efavirenz	1 (5%)
Emtricitabine/tenofovir + raltegravir	4 (20%)
Emtricitabine/tenofovir + dolutegravir	4 (20%)
Emtricitabine/tenofovir + efavirenz	1 (5%)
Ritonavir + epivir + atazanavir	1 (5%)
Ritonavir + abacavir/lamivudine + atazanavir	1 (5%)
Ritonavir + abacavir/lamivudine + raltegravir	1 (5%)

BCCA, British Columbia Cancer Agency; IPI, international prognostic index; ECOG, Eastern Cooperative Oncology Group; CNS, central nervous system; HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy.
*BCCA low risk has Ann Arbor stage I, II, or III, bulk <5 cm and normal lactate dehydrogenase (LDH) level; all others are high risk.
†Magrath low risk has ≤1 extranodal site of BL and LDH ≤350 IU/l; all others are high risk.
‡Only patients with meningeal disease were considered, while patients with intraparenchymal brain lesions were excluded.
§Patients receiving HAART at the time of lymphoma diagnosis had asymptomatic HIV infection, with undetectable HIV-RNA plasmatic levels in 11 patients and a median CD4$^+$ cell count value of 337 (range 227–560 cells/μl).
¶Diagnoses of HIV infection and Burkitt lymphoma were concomitant in seven patients, with a median HIV-RNA level of 203 417 copies/ml (range 7205–1 044 652), and a median CD4$^+$ cell count value of 183 (range 36–272 cells/μl).

($n = 3$), and peripheral blood smears and flow cytometry ($n = 2$). Seven (35%) patients had HBV and/or HCV infection. Details of HAART, HIV-RNA plasmatic levels and $CD4^+$ cell counts at the time of lymphoma diagnosis are summarised in (Table III).

Feasibility and toxicity

Eighteen patients completed the induction (median duration: 47 days; IQR 41–54); two patients died of sepsis by *Stenotrophomonas maltophilia* and *Pneumocystis carinii* respectively. Drug doses were reduced in four patients and methotrexate and etoposide occasionally required delivery delay due to transaminase increase or neutropenia. HAART was transiently discontinued in three patients due to increase of transaminases ($n = 2$) and pancreatitis; all of them completed the planned chemoimmunotherapy. Haematological toxicity during induction was common, but manageable (Table IV): grade 4 neutropenia and thrombocytopenia occurred in 18 (90%) and 11 (55%) patients, respectively, grade 4 bacterial infections occurred in one (5%) patient; no systemic fungal infections were recorded. Only two episodes of grade 4 non-haematological toxicity (hepatotoxicity and mucositis) were recorded (Table IV). Tumour lysis syndrome occurred in one patient, followed early by normalisation of biochemical exams.

Toxicity of the consolidation phase was mild and manageable (Table IV), with the exception of neutropenia (11/18) and thrombocytopenia (12/18), no cases of grade 4 toxicity were recorded. Twelve patients were referred to autologous stem cell collection, which was successful in all cases, with a median of $7{\cdot}6 \times 10^6$ $CD34^+$ cells/kg (range $3–36 \times 10^6$); stem cell collection was not indicated in six patients who achieved CR after induction. Engraftment was successful, in the expected times, in the five transplanted patients; usual toxicities of myeloablative chemotherapy were recorded in these patients. Patients with HBV or HCV infections did not experience grade 4 hepatotoxicity, and completed the planned therapeutic programme without interruptions. There was a single case of second cancer; a 46-year-old woman developed a histiocytic sarcoma in the right iliac lymph nodes after 20 months from CARMEN treatment; the histiocytic sarcoma was resected and irradiated; the patient is alive and free of relapse from both tumours at 88 months of follow-up.

The median duration of the whole programme of the 18 patients who received the planned treatment was 68 days (IQR: 62–74). The duration of the whole programme was 117–135 days for the five patients treated with ASCT.

Activity and efficacy

After induction, 18 patients achieved an objective tumour response (ORR = 90%; 95% CI = 77–100), no patient experienced progressive disease. Eleven patients had a radiologic and metabolic CR; five patients had PET-positive residual areas concomitant to pathologic images at contrast-enhanced CT scan that regressed after further treatment (consolidation and ASCT); and two patients had PET-positive areas without residual images at contrast-enhanced CT scan that remained unchanged after further treatment (consolidation and ASCT) and at least for two years after treatment conclusion. After complete revision of imaging, the latter two patients were considered as false PET positivity and in CR after induction. Accordingly, response to induction course was complete in 13 patients (CRR = 65%; 95% CI = 45–85%) and partial in five. All responders received consolidation, and five of them received ASCT. At the end of the whole therapy, 14 patients

Table IV. Grade 3–4 toxicities following induction and consolidation phases

	Induction ($n = 20$)		Consolidation ($n = 18$)	
Type of toxicity	Grade 3	Grade 4	Grade 3	Grade 4
Haematologic*				
Neutropenia	2 (10%)	18 (90%)	4 (22%)	11 (61%)
Anaemia	10 (50%)	1 (5%)	4 (22%)	0 (0%)
Thrombocytopenia	2 (10%)	11 (55%)	3 (17%)	12 (67%)
Infections				
FN/bacterial infections†	5 (25%)	1 (5%)	1 (5%)	0 (0%)
CMV reactivation	2 (10%)	0 (0%)	0 (0%)	0 (0%)
Hepatotoxicity	1 (5%)	1 (5%)	0 (0%)	0 (0%)
Gastrointestinal				
Mucositis	6 (30%)	1 (5%)	0 (0%)	0 (0%)
Diarrhoea	1 (5%)	0 (0%)	0 (0%)	0 (0%)
Neurotoxicity	1 (5%)	0 (0%)	0 (0%)	0 (0%)

FN, febrile neutropenia; CMV, cytomegalovirus.

*All patients but one needed recombinant human granulocyte colony-stimulating factor (rHuG-CSF), mostly after methotrexate (day 21) and etoposide (day 15) delivery.

†Two patients experienced septic shock and died of infection complications during induction.

achieved an objective response, which was complete in all of them (CRR = 70%; 95% CI = 50–90%).

At a median follow-up of 55 (41–89) months, there were six events: four patients experienced progressive disease immediately after consolidation and two died of bacterial infections during induction; 14 patients remain relapse-free, with a five-year PFS of 70% (95% CI = 60–80). The four patients with progressive disease received intensification and ASCT (Table II): three of them died of lymphoma, while the last one achieved a durable remission and is alive at 77 months of follow-up. No patient experienced relapse/progressive disease in the central nervous system (CNS). Among the five patients with CSF/meningeal disease at presentation, one experienced lymphoma progression outside the CNS, one died of bacterial infection during induction and the other three are alive and relapse-free at 43–55 months. Interestingly, the four patients with HGBL and double-hit lymphoma had responsive disease, receive consolidative ASCT and are alive and relapse-free at 43+, 48+, 51+ and 89+ months respectively. Fifteen patients are alive, with a five-year OS of 75% (95% CI = 66–84; Fig 2).

Discussion

The proposed therapy assessed in the CARMEN trial was associated with encouraging results and acceptable safety profile in HIV/AIDS patients with high-risk BL or HGBL. This trial demonstrates the reproducibility of the attained survival figures in a multicentre setting. In fact, the present results reproduce findings reported in the pilot retrospective experience[9] and in HIV-negative patients with BL treated with the same combination, where CRR and two-year PFS were 77% and 68% respectively.[7] The efficacy of this short-term combination is similar to those attained with more demanding and resource-consuming regimens,[6,10,17,19,2,13,21] with an apparently better tolerability profile (Table V). Although addressed in a few cases, efficacy of the CARMEN programme in patients with HGBL is an important issue as this is a lymphoma entity poorly investigated in HIV-positive subjects. Patients with this lymphoma, including a patient with double-hit lymphoma, remain relapse-free at 43–89 months of follow-up, which contrasts with the poor results reported with R-CHOP in HIV-negative patients with these lymphomas.[5] These favourable safety and efficacy profiles support the use of the CARMEN combination both in HIV-positive and -negative patients with BL or HGBL.

This trial has a few limitations. In particular, the relatively small sample size could have introduced a favourable selection bias. However, the prospectively estimated sample size was large enough to confirm that the activity and efficacy of the CARMEN programme are comparable to those reported with previously published treatments, with some tolerability and duration advantages, and was in line with the study size of prior prospective trials in the rituximab era (n = 11–34; Table V). Moreover, most registered patients had unfavourable features, and all of them had high-risk lymphomas according to three widely accepted risk scores, which excludes *bona fide* a favourable selection bias. Overall, these findings support the qualitative and quantitative suitability of the study population to draw reliable conclusions on this short-term therapy in multicentre setting. Importantly, the CARMEN trial exhibits some strengths related to the central pathology review and the fact that diagnostic tissue samples of every enrolled patient were assessed by FISH for *MYC*, *BCL-2* and *BCL-6*, which allowed us to define lymphoma entities according to modern diagnostic criteria.

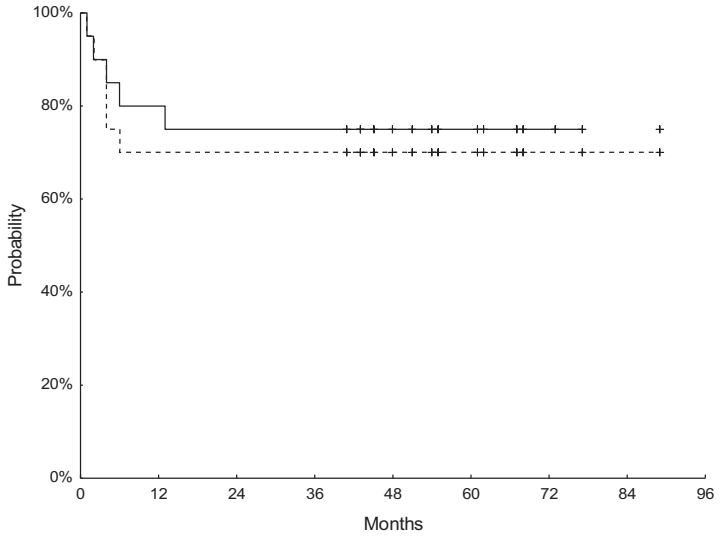

Fig 2. Progression-free (dotted line) and overall (continuous line) survival curves of the whole series.

Table V. Prior studies on the treatment of HIV-positive patients with Burkitt lymphoma and high-grade B-cell lymphoma

Ref.	Type	Regimen	Rituximab	N°	Median (range) age (years)	CNS disease (%)	Planned treatment (days)	TRM (%)	Severe infections (%)	Fungal infections (%)	Mucositis (%)	Incomplete treatment[ε] (%)	Median follow-up (months)	CRR	Two-year PFS	Two-year OS
(Cortes *et al.*, 2002)[6]	P	Hyper-CVAD	No	13α	43 (32–55)	0	147	15	92	23	0	77	29	92	DFS: 52	48
(Oriol *et al.*, 2005)[16]	P	PETHEMA-LAL3/97-GMALL	No	19	41 (23–65)	17	131	21	24	NR	21	68	31	68	DFS: 71	46
(Galicier *et al.*, 2007)[10]	P	LMB86	No	63β	40 (20–57)	76	175	11	59	16	NR	25	66	70	51	47
(Wang *et al.*, 2003)[24]	R	CODOX-M/IVAC vs. others	No	14	41 (19–61)	21	112	13	38	NR	75	14	34[δ]	63	60	NR
(Rodrigo *et al.*, 2012)[19]	R	CODOX-M/IVAC	Yes/No	14	46 (32–56)	NR	112	0	36	0	21	43	12	86	NR	83
(Barnes *et al.*, 2011)[2]	R	CODOX-M/IVAC	Yes/No	14	46 (17–78)	19	112	7	14	NR	NR	NR	NR	93	3-yr: 68	3-yr: 68
(Oriol *et al.*, 2008)[17]	P	PETHEMA-LAL3/97-GMALL	Yes	19	39 (29–54)	5	168	16	26[γ]	21	27	32	22	84	DFS: 87	73
(Noy *et al.*, 2015)[14]	P	Modified CODOX-M/IVAC	Yes	34β	42 (19–55)	11	168	3	38	5	9	15	26	NR	69	69
(Dunleavy *et al.*, 2013)[8]	P	DA-EPOCH	Yes	11	44 (24–60)	0	126	0	10	0	9	0	73	91	92	92
(Montoto *et al.*, 2010)[13]	R	CODOX-M/IVAC	Yes	30	38 (28–69)	17	112	17	64[γ]	0	12[γ]	30	22	70	88	62
(Roschewski *et al.*, 2020)[20]	P	DA-EPOCH	Yes	28ζ	49 (18–86)	10	126	4	25	NR	19	18	59	NR	5-yr: 85	NR
(Alderuccio *et al.*, 2020)[1]	R	Varied	Yes	142	44 (23–77)	28	≥112	13	NR	NR	NR	NR	44	71	3-yr: 60	3-yr: 66
Present	P	CARMEN program	Yes	20β	42 (26–58)	25	73	10	10	0	5	10	55	75	5-yr: 70	5-yr: 75

CNS, central nervous system; TRM, treatment-related mortality; CRR, complete remission rate; PFS, progression-free survival; OS, overall survival; P, prospective trial; R, retrospective study; NR, not reported (for the whole series or for HIV-positive patients); DFS, disease-free survival; HIV, human immunodeficiency virus.

α Only six patients had HIV-related Burkitt lymphoma.

β Some lymphoma entities other than Burkitt lymphoma were considered.

γ Toxicity expressed in number of courses.

δ Median follow-up of both HIV-negative and HIV-positive patients.

ε Treatment termination due to reasons different from progressive disease.

ζ Data reported in the table regards a whole series of 113 patients (28 were HIV-positive patients) with Burkitt lymphoma. Data from HIV-positive patients have not been reported separately.

Results achieved with the CARMEN chemoimmunotherapy are similar to those reported with the other three regimens investigated in prospective HIV-BL trials in the rituximab era: CODOXM-IVAC,[14] GMALL[17] and da-EPOCH.[20] However, these trials are incomparable because they used different selection criteria, with variable proportions of patients having lymphoma entities different from BL, CNS involvement or requiring ASCT. The recent multicentre prospective trial addressing da-EPOCH in patients with newly-diagnosed BL included 28 HIV-positive patients.[20] Although tolerability and feasibility data have not been reported separately for this subgroup of patients, the expounded four-year event-free survival of 85% is an impressive achievement. However, a recent study performed on the largest retrospective cohort of HIV-positive patients with newly-diagnosed BL (n = 142) suggests that these results are hardly achievable in real life, where da-EPOCH-R has been associated with a three-year PFS of only 51%, which is significantly poorer with respect to the 74% achieved with CODOXM-IVAC in the same participating centres.[1] In particular, results of da-EPOCH-R were poor in the subgroup of patients with CSF/meninges involvement, both in the prospective and retrospective study, with a three-year event-free survival of 45%[20] and 33%[1] respectively. Interestingly, none of the patients enrolled in the CARMEN trial experienced progressive disease in the CNS and three of the five patients with CSF involvement at presentation are alive and relapse-free at 43–55 months of follow-up.

In comparison with previously reported combinations, the CARMEN programme showed some strengths and weaknesses that deserve to be discussed. Short duration, good acute tolerability and low rates of mucositis, opportunistic infections and other acute and late complications, as well as low costs are the main advantages of this proposed therapy. The CARMEN programme was delivered in a shorter period (median 68 days; IQR: 62–74) than other regimens, which should be delivered between 112 and 168 days (Table V). A few days of delay were due mostly to neutropenia, but overall haematological toxicity was manageable. No toxic events were recorded in the seven (35%) patients with HBV and/or HCV infection, a common condition in HIV/AIDS patients that is often related to increased toxicity and limited efficacy. Importantly, all registered patients but two completed the treatment protocol, which compares favourably with prior prospective studies that have reported treatment interruption in 25–77% of patients, mostly due to severe bacterial and fungal infections (16–23% of cases; Table V). Another advantage of the CARMEN programme regards a potentially lower risk of infertility and cardiac toxicity, which is an important issue considering that these are usually young patients with high probabilities of cure. In fact, this treatment includes only two doses of cyclophosphamide and a single dose of doxorubicin (Table I) , two drugs that are used in larger amounts in cyclic regimens like CODOX-M/IVAC, DA-EPOCH, LMB, BFM and HOVON, often in combination with ifosfamide, melphalan and/or carmustine.[15] Although this trial was not designed to assess cost effectiveness, we can hypothesise that a short-term regimen, without expensive target drugs, with a lower incidence of severe infective complications, and exceptional need for intravenous antibiotics and antifungal drugs should be associated with lower costs.

The CARMEN programme exhibits some weaknesses, in particular related to the frequent use of ASCT. Per protocol, patients with PR after the induction course received a high-dose-cytarabine-based consolidation followed by BEAM-conditioned ASCT. Five patients received ASCT; all of them achieved a CR and remained relapse-free for 41–77 months. However, two of these patients had a PET positivity with a negative CT scan after induction that remained unchanged for at least two years; thus, revision of patients' imaging led us to consider these patients as complete responders to induction, and, per protocol, they should not have received an ASCT. These facts confirm the risk of false-positive results of PET in HIV-positive patients with aggressive lymphomas and their critical effects on therapeutic decision. This is a well-known issue in patients with BL, where the positive predictive value of PET is only 20%, both in children and adults.[3,18] On these notions, we recommend to perform pathological confirmation of PET-positive residual areas in the case the indication for ASCT is based on PET-related response definition.[9,15]

In conclusion, the CARMEN programme achieved the primary endpoint in HIV/AIDS patients with high-risk BL and HGBL treated in a multicentre setting. With respect to previously reported regimens, the proposed programme was delivered in a shorter period, with a better tolerability profile, a single case of mucositis and without fungal infections. This therapeutic strategy was effective also in a few patients with meningeal dissemination, a feature associated with a significantly poorer prognosis. Given its excellent survival effect and good safety profile, the CARMEN programme deserves to be assessed in a randomised trial against one of the previously reported regimens. In the meantime, this strategy should be considered in routine practice in HIV/AIDS patients with high-risk BL and HGBL, and investigated in other lymphoma entities.

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Author contributions

AJMF, GR, MS and AR designed the research study. FF and MP performed the central pathology review. LP contributed essential reagents and performed cytogenetic exams. CC, AL, LV, BA, MF, DF, LR, GD, LF, MS and TC registered and treated patients and collected clinical data. AJMF, GR, MS and AR analysed the data and wrote the paper.

Conflicts of interest

The authors have no competing interests.

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