Manuscript title: Efficacy and toxicity of PACEBOM chemotherapy in relapsed/refractory (R/R) aggressive lymphoma in the rituximab era

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Abstract

Title: PACEBOM in relapsed/refractory (R/R) aggressive lymphoma in the rituximab (R) era.

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Background: R/R aggressive lymphoma outcomes are poor. There is no standard treatment. PACEBOM has shown efficacy for several lymphoma subtypes in published reports. We evaluate PACEBOM+/-rituximab for R/R aggressive lymphomas in this millennium.

Methods: In this retrospective, single-centre study, R/R aggressive lymphoma patients who received PACEBOM (prednisolone, doxorubicin, cyclophosphamide, etoposide, bleomycin, vincristine, methotrexate) or its derivatives were identified from the pharmacy database. Demographic, treatment, toxicity and survival data were collected.

Results: 37 eligible patients were identified. Histological subtypes included 20 DLBCL, 10 TCL, and 7 HL. All DLBCL patients had received prior rituximab. 31 (84%) received 2nd line PACEBOM. Median number of cycles was 6 (1-6). 18/20 B-cell lymphoma received R-PACEBOM. Overall response rate (ORR) was 65%, 70% and 71% in patients with DLBCL, TCL, and HL respectively. 13 patients underwent ASCT post-PACEBOM. Median follow-up was 49 months (m) (3-201). Most common grade 3-4 toxicities were neutropenia (46%), anaemia (24%) & thrombocytopaenia (16%). No additional toxicity was seen in patients who received rituximab.

Conclusion: In this cohort, PACEBOM is active in R/R aggressive lymphoma with manageable toxicity and can be safely combined with rituximab. Outcomes were similar to reports of other salvage regimens. PACEBOM remains a suitable option for R/R aggressive lymphoma, in patients exposed to prior rituximab & those planned for ASCT.

Background

Lymphoma comprises almost 5% of all new cancers.[1, 2] Combination chemotherapies such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) +/- rituximab for most indolent and aggressive NHL (non-Hodgkin lymphoma) and ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) for Hodgkin lymphoma (HL) are standard first-line treatment options. Whilst most patients with high-grade lymphomas, achieve complete remission with first-line chemotherapy, a significant proportion will relapse and eventually die of disease. Following relapse, most patients remain sensitive to chemotherapy but less than 10 percent experience prolonged disease free survival.[3] There are no standard chemotherapy combinations in the relapsed setting and various regimens have acceptable efficacy in this setting including gemcitabine, ifosfamide and platinum based combinations as well as bendamustine.[4-7] PACEBOM (prednisolone, doxorubicin, cyclophosphamide, etoposide, bleomycin, vincristine, and methotrexate) and its derivatives such as PMitCEBO (prednisolone, mitoxantrone, cyclophosphamide, etoposide, bleomycin, and vincristine) have been utilized for decades in pre-rituximab era due to promising efficacy.[8] However, they have been more recently replaced by infusional regimens such as DHAP and ICE, with no randomized data supporting superiority of these newer regimens over PACEBOM.[9,10] High-dose chemotherapy followed by autologous stem cell transplant (ASCT) is an accepted treatment for selected relapsed/refractory lymphomas in transplant eligible patients, and provides a second chance at cure for some cases of high-grade lymphoma.[11] However, many patients are deemed unsuitable for transplant due to age or comorbidities. Only two randomised trials have compared chemotherapy regimens in R/R lymphomas, both in DLBCL and published recently. The CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) trial compared R-ICE (rituximab, ifosfamide, cisplatin, and etoposide) with R-DHAP (rituximab, dexamethasone, high-dose cytarabine, cisplatin) in 400 patients, many of whom had not received prior rituximab, and

in the NCIC-CTG LY.12 trial, 619 patients were assigned to GDP (gemcitabine, dexamethasone, cisplatin) or DHAP.[12, 13] Neither of these trials yielded superior outcomes with a particular regimen. R/R high-grade lymphoma in patients ineligible for transplantation is particularly challenging and is associated with a markedly reduced survival.[14]

PACEBOM was developed in 1991 by Sweetenham *et al.* in an attempt to improve efficacy and avoid the toxicity of first-line MACOP-B (methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) in aggressive B-cell lymphomas.[15] The regimen was well tolerated, and in a small study of 61 patients with advanced lymphoma of various subtypes. [16]

A subsequent randomised phase III study demonstrated equivalent efficacy of PACEBOM to CHOP in the pre-rituximab era, and PMitCEBO and PACEBOM have proven efficacy in several pre-rituximab studies of relapsed aggressive lymphomas.[16-19] However, studies evaluating PACEBOM were mostly conducted over 2 decades ago, prior to routine use of modern regimens including ABVD and R-CHOP. It is known that the addition of rituximab to chemotherapy improves survival in multiple B-cell lymphomas, [20, 21] and is safely combined with most regimens but no data are available for rituximab in combination with PACEBOM. In addition, its efficacy and safety profile if given after ABVD or CHOP are not widely reported. While there are numerous targeted therapies with promising efficacy, they are not readily accessible in many countries outside the context of a clinical trial. PACEBOM offers an additional, affordable, outpatient-delivered option in the management of relapsed aggressive lymphoma, particularly for those not able to tolerate the toxicity of an infusional regimen. In this context, our single-centre retrospective analysis evaluated the efficacy and toxicity of PACEBOM with or without rituximab for R/R aggressive lymphoma over a ten-year period.

Method

Patients and study design

Patients were deemed eligible if they were 18 years or over, had a histologically confirmed diagnosis of aggressive lymphoma, documented relapse after receiving 1 or more prior lines of systemic treatment and received at least 1 cycle of PACEBOM or PACEBOM-like chemotherapy (PMitCEBO, PACE-OM, P-CE2BOM) during the study period. Patients were identified from the hospital pharmacy database at a single institution over a 10-year period between 1 January 2004 and 31 September 2014. Patient demographics, treatment details and toxicity data were collected from hospital medical records. All radiology was reviewed where available and radiology reports obtained in those patients with no films available. Elderly patients (>70years) and those with prior cardiac history underwent baseline left ventricular ejection fraction (LVEF) evaluation (echocardiogram or gated-cardiac blood pool scan) and only patients with no significant cardiac history or stable cardiac disease and normal LVEF were eligible for inclusion of doxorubicin in the PACEBOM regimen (i.e. doxorubicin was omitted in those with poor cardiac function). The study was approved by the local institutional review board. (EH LR 76.1314 version 2)

Chemotherapy

PACEBOM was administered as per published studies [15] and consisted of prednisolone 50mg daily for four weeks, then alternate days for 8 weeks. Doxorubicin 35mg/m² intravenous (IV), cyclophosphamide 300mg/m² IV, and etoposide 150mg/m² IV are delivered on day one every second week, alternating with bleomycin 10000 IU/m², vincristine 1.4 mg/m² (maximum 2mg), and methotrexate 50mg/m²

combination, administered on day 8. The total planned chemotherapy course was 12 weeks.[16] When clinically indicated, a modified PACEBOM regimen occurred with a change in dose or omission of one or more of the chemotherapy agents. All treatment was given in a dedicated chemotherapy day unit.

Follow up

Tumour response to chemotherapy was assessed according to the modified International Working Group (IWG) criteria for response in lymphoma.[22] All patients were followed up at least for 6 months after treatment completion.

Registered clinical adverse events alongside major haematological and biochemical toxicities were recorded from medical records during the treatment period and for 30-days subsequent to completion. CTCAE (Common Terminology Criteria for Adverse Events) version 4.0 was used to grade adverse events.

Statistical analysis

Descriptive statistics were used to analyse demographics and baseline characteristics. Median follow up was calculated from the date of diagnosis to the last follow up or death if known. Initial disease free survival (DFS) was calculated from the date of completion of first line chemotherapy to the date of the first relapse. Progression free survival (PFS) after PACEBOM was calculated from the date of the first cycle of PACEBOM to documented relapse or first dose of next line of chemotherapy, death from any cause or last known follow up. Total overall survival (OS) and PACEBOM-related OS were defined from date of diagnosis or first day of PACEBOM respectively until documented death or last known follow up. OS, DFS and PFS were analysed using the Kaplan-Meier method.

Results

Thirty-seven patients were treated with PACEBOM for biopsy-proven relapsed aggressive lymphoma between 1 January 2004 and 31 September 2014. Thirty-one patients (84%) were male and median age at diagnosis was 59 years. Baseline demographics and first-line chemotherapy details are summarised in table 1.

Thirty-one patients (84%) received PACEBOM as second-line therapy and 6 (16%) had received two or more prior regimens. Twenty-three of 30 NHL patients received first-line CHOP +/- R, with all 20 DLBCL patients receiving prior rituximab and all 7 HL patients received first-line ABVD. Sixty-two percent (23/37) of patients achieved complete remission (CR) after first line treatment, 16/20 DLBCL, 4/7 HL and 3/10 TCL while four patients had primary refractory disease (2/20 DLBCL, and 2/10 TCL). Of the 31 patients who received second-line PACEBOM, 42% achieved complete response (7/17 DLBCL, 3/6 HL, and 3/8 TCL).

A total of 167 cycles of PACEBOM were delivered with a median number of six cycles. Eighteen of 20 (90%) patients with B-cell NHL received rituximab in combination with PACEBOM. All 20 patients had received prior rituximab. Details of PACEBOM chemotherapy are summarised in table 2.

Median follow up for the whole cohort was 49 months (range 33-201 months). Sixteen patients remained alive at the end of the study period, 13 of whom were disease-free and 3 having documented relapse or progression. Nineteen patients (52%) had died at the time of analysis. Cause of death in 80% (15/19) was lymphoma. Two patients died of treatment-related sepsis, two patients died subsequent to transplant; GVHD in one patient, and one unknown. Two patients were lost to follow up. Details of the patients' treatment and follow up outcomes are summarised in figure 1.

In DLBCL patients, median PACEBOM PFS was 6.4 month (95% CI 0-15), and median OS 12.2 (95% CI 0-25) months. ORR in DLBCL patients was 65% (13/20).

Complete response to PACEBOM was achieved in 17 patients, and CR rates were at least 40-50% in all disease subtypes, nine patients had partial response (PR) and eight patients progressed after PACEBOM chemotherapy. Details of response according to disease and line of therapy are in table 3.

Thirteen patients (7 DLBCL, 5 HL, and 1 TCL) underwent successful stem cell harvest and transplant after achieving CR to PACEBOM. Twelve out of 13 patients had confirmed CR post ASCT and one patient achieved PR. Four additional patients underwent a subsequent line of chemotherapy before proceeding to ASCT. Only two patients failed to stem cell harvest post-PACEBOM with one patient having received intense first-line therapy (CHOP/CEOP) and bone marrow involvement with lymphoma cells in both of those patients.

PACEBOM-related toxicity is summarised in table 4a and 4b. Treatment was delayed on 21 occasions and 23 patients had a dose reduction or dose omission. Bleomycin and methotrexate were the most commonly omitted drugs. Bleomycin omitted mainly due to pulmonary toxicities and methotrexate due to deranged LFTs and mucositis. Fifty percent (19/37) of the patients required red blood cell transfusions and rate of platelet or GCSF support was 20%. Haematological toxicities (anaemia, thrombocytopenia and neutropenia) and stomatitis were the most common grade 3 and 4 adverse events. Two treatment-related deaths occurred, both due to febrile neutropenia. PACEBOM was ceased entirely in another two patients, both following cycle 1, due to severe heart failure and severe mucositis respectively. Cumulative dose of anthracyclines was not greater than the recommended lifetime dose of 550mg/m² in any patient.[23] In our study majority of the patients received CHOP (doxorubicin 300mg/m²) followed by PACEBOM (doxorubicin 210mg/m²) and cardiac toxicity was observed only in one patient with underlying cardiac failure. Only one patient in our cohort had significant cardiac toxicity which was received R-CEOP (etoposide replacing doxorubicin) as first-line treatment. R-

CEOP was stopped due to an acute myocardial infarction. Treatment was changed to P-CE2BOM (non-anthracycline containing regimen) and the patient only received one cycle of BOM which also was ceased due to new presentation of low ejection fraction and severe heart failure. Given the patient received no anthracycline, the heart failure was thought to be due to the acute coronary syndrome, rather than chemotherapy. Of note, with median 49 (33- 201) months follow up, no patient had anthracycline-induced cardiomyopathy.

Discussion

PACEBOM chemotherapy was initially developed as first-line treatment of aggressive lymphoma two decades ago.[15] The majority of data relating to the efficacy and toxicity are from the early 1990's, prior to the establishment of ABVD for previously untreated HL and first-line CHOP +/- Rituximab for high-grade NHL.[20, 24] Despite early data from large-scale trials demonstrating promising efficacy with tolerable toxicity in both first-line and relapsed disease, it has not been widely adopted and published data in the rituximab era are scant, particularly in patients who have received prior anthracycline-containing regimens such as CHOP or ABVD.

In our study, PACEBOM +/- rituximab was used in relapsed/refractory high-grade lymphomas as a salvage regimen before ASCT and as a palliative regimen after failure of one or more chemotherapy regimens. Complete responses were seen in at least 40% of cases across all lymphoma subtypes and a high rate of stem cell collection and ASCT in patients deemed eligible was achieved.

Previous randomised studies evaluating PACEBOM describe efficacy comparable to CHOP and MACOP-B in untreated NHL and HL.[8, 16, 25] A similar regimen, PMitCEBO also demonstrated equivalent efficacy to CHOP in a phase III of 784 aggressive NHL patients aged 60 or over [18] with ORR of 84% versus 83%, 3-year failure-free survival (FFS) 42% versus 44%, and 3-year OS 45% versus 46%. PMitCEBO yielded an ORR of 75% with a median duration of response of 12 months (range 1-27) in a study of 20 NHL patients.[19]

The ORR in our cohort of DLBCL patients was 65%. This is comparable to relapsed DLBCL patients enrolled in the phase III CORAL who received R-DHAP or R-ICE (63% in both arms).[9] Another randomised phase III study, reported ORR of 44% with DHAP and 45.2% with GDP.[4, 13] Another gemcitabine-containing regimen, GEMOX is associated with ORR of 45-78% and 50-63% of patients proceeding to ASCT.[10]

The majority of HL patients respond to upfront treatment with ABVD. First-line PACEBOM was evaluated in 86 previously untreated HL patients with 5-year OS of 90%, failure-free survival (FFS) of 64% and ORR of 88%. This treatment was well tolerated and fertility was preserved.[16] No data have been reported for PACEBOM in R/R HL after ABVD to our knowledge however 71% of R/R HL in our study responded to PACEBOM and median OS was 15 months (95% CI 2-28). Six of the seven HL patients underwent successful ASCT after PACEBOM. In other reports of salvage chemotherapy including ICE, miniBEAM, GDP, GEMOX and GEM-P, ORR ranged between 50-80% with similar ASCT rates.[26-28] No randomised studies comparing chemotherapy regimens in R/R HL has been reported to date.

PACEBOM toxicities reported in our study are consistent with other regimens for R/R lymphoma, acknowledging our data is retrospective. PMitCEBO was associated with more frequent grade 3-4 haematological toxicity compared to CHOP in the first-line phase III trial (63% versus 42%) mainly due to more leucopenia. Twelve patients (3-6% in each arm) died

from infection. In the CORAL trial 16% experienced grade 3-4 febrile neutropenia with an additional 7% reporting grade 3/4 non-neutropenic infection. There were 4 infection-related deaths (3 in R-DHAP arm).[12] Rates of grade 3/4 haematological toxicities in our patients were comparable (46% neutropenia, 19% febrile neutropenia).

Cardiomyopathy is a concern in patients receiving 2 lines of therapy including anthracycline. Recommended maximum lifetime doxorubicin dose is 450-550mg/m². [23] The standard dose at our institution is 6 cycles of CHOP (total, 300mg/m² of doxorubicin) and ABVD (maximum 6 cycles, or 12 treatments, 25mg/m² in each cycle-also 300mg/m² total dose). Patients in our cohort received maximum of 6 cycles of PACEBOM equating to 210mg/m² of doxorubicin. Total lifetime doxorubicin dose is therefore 510mg/m² in patients who receive 6 cycles of PACEBOM after CHOP or ABVD, which falls within the recommended maximum dose of <550mg/m². Of note, with median 49 (33- 201) months follow up, no patient had anthracycline-induced cardiomyopathy.

Platinum agents in regimens such as GDP or DHAP can cause significant renal impairment. In patients with normal baseline renal function in the CORAL study, grade 3/ 4 renal toxicity occurred in 6% with R-DHAP.[9] In our study only 2/37 (5%) patients had grade 3 renal impairment, with no grade 4 events, both in the context of aggressive TCL and concurrent sepsis.

In contrast to many infusional regimens used in R/R lymphoma, PACEBOM is delivered weekly, in an outpatient setting and exposes patients to a greater number of active anti-lymphoma drugs without significant additional toxicity. It provides the option to substitute contraindicated drugs such as anthracyclines and methotrexate while maintaining efficacy and the favorable toxicity profile makes it appealing for patients who may be unsuitable for more

intensive regimens due to advanced age, comorbidities or a desire to avoid lengthy inpatient stays. Newer combinations such as gemcitabine-containing regimens and bendamustine have been developed but few have been analysed in large phase III studies and none have been compared to PACEBOM despite the robust efficacy seen in early trials.

With the advent of novel agents, it is unlikely that a prospective study will be done in R/R lymphoma in all of the included histological subtypes. Newer targeted agents are proving extremely promising for all types of lymphoma, however in many countries, these are not yet available in clinical practice due to the prohibitive cost, and the lack of approval based on early study results which currently provide limited evidence in validated endpoints such as overall survival. There is no doubt these will become available in the future, however, until such a time that their role is established in clinical practice, PACEBOM +/- R provides another line of therapy for patients with R/R lymphoma.

Conclusion

In this cohort, responses to PACEBOM regimen were seen across all three subtypes with manageable toxicities, but analysis in larger cohorts of each of these lymphoma types is warranted. PACEBOM can be safely combined with rituximab in B-cell lymphoma, has efficacy in patients exposed to previous ABVD, CHOP and rituximab and allows successful stem-cell harvest and ASCT in appropriate patients. In our study, we report very similar outcomes to other currently used regimens in R/R aggressive lymphomas. PACEBOM with or without rituximab should remain a treatment option for R/R lymphoma in the absence of available novel agents.

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Figure 1. Patients' outcome

Table 1. Patient Characteristics.	N=37 (%)
Median age at diagnosis (range)	59 (range 22-81)
Gender	
Male	31 (83)
Female	6 (17)
Lymphoma subtype	
NHL	30 (81)
DLBCL	20 (54)
TCL	10 (27)
HL	7 (19)
Stage at diagnosis	
I	0
II	10 (27)
IIA	8
IIB	2
III	12 (32)
IIIA	8
IIIB	4
IV	15 (41)
IVA	5
IVB	10
Extranodal sites	16 (43)
Initial treatment	
CHOP +/- R	23 (62)
ABVD	7 (19)
Chlorambucil + VPP	1 (3)
CEOP/CHEOP/EPOCH	4 (11)
Radiotherapy	2 (5)
Rituximab prior to PACEBOM	20/20 (B-cell NHL)
Response to initial treatment	
CR	23 (62)
PR	10 (27)
PD	4 (11)

Table 2. PACEBOM treatment details	Total N=37 (%)
Line of PACEBOM chemotherapy	
2nd line	31 (84)
Received rituximab in combination	18
≥ 3rd line	6 (16)
Received rituximab in combination	2
Total lines of Chemotherapy	
2	14 (38)
3	16 (43)
≥4*	7 (19)
Subsequent lines of Chemotherapy post PACEBOM	
0	23 (62)
1	8 (22)
2	3 (8)
≥3	3 (8)
Subsequent chemotherapy + ASCT	12 (32)
Allograft	1 (3)
Total number of cycles given	167
Median	6 (range 1-6)
All patients with stem cell transplant	17
Stem cell harvest post PACEBOM	13
CR	12
PR	1
Planned ASCT	1
ASCT conditioning regimen	
BEAM	12
LACE	2
Other	3
Reason for no ASCT	
Complete remission post-chemotherapy	2
Progressive/refractory disease	9
Failed harvest	2
Not fit	4
Unknown	3
Final follow-up	
Patients still alive	16 (43)
CR	13

PD	3
Lost to follow up	2 (5)
Died	19 (52)
Cause of Death	
Disease	15 (80)
Treatment-related	
Sepsis	2
Transplant related (GVHD)	1
Unknown	1
* 6 patients received ≥ 5 lines of chemotherapy	

Table 3. PACEBOM outcomes *

Disease	CR (%)	PR (%)	PD (%)	ORR (CR+PR) (%)	Unable to assess
All patients	17 (46)	9 (24)	8 (22)	50/69 (70)	3 (8)
DLBCL (n=20)	10 (50)	3 (15)	4 (20)	13/20 (65)	3 (15)
TCL	4 (40)	3 (30)	3 (30)	7/10 (70)	0
HL	3 (43)	3 (29)	1 (14)	5/7 (71)	0
Line of therapy					
2 nd line	13 (42)	8 (29)	7 (22)	21 (71)	3 (7)
3 rd line or above	3 (50)	1 (17)	2 (33)	17 (67)	0
* Modified Cheson 2007 (IWG response criteria for lymphoma)					

Table 4a. Toxicity			
Toxicity	All grades (%)	G1-2 (%)	G≥3 (%)
Anaemia	71	46	24
Neutropenia	57	11	46
Febrile neutropenia	19	-	19**
Thrombocytopenia	43	27	16
Renal impairment	26	21	5
Hepatic toxicity	29	24	5
Non-neutropenic infection	8	3	5
Peripheral neuropathy	8	5	3
Nausea & vomiting	53	53	0
Fatigue	58	53	5
Stomatitis	43	27	16
Constipation	39	39	0
Diarrhoea	14	14	0
Insomnia	3	3	0
Other serious toxicity			
SMV thrombosis	3	0	3
DVT	5	5	0
Cardiac toxicity*	3	0	3
Mucositis*	3	0	3
* Chemotherapy ceased after cycle 1 for these two patients.			
**Two patients had G5 febrile neutropenia			

Table 4b. Toxicity	
Number of treatment delays	21
Number of reductions	13
Cytopenia	7
Peripheral neuropathy	2
Other	4
Number of dose omission	20
Methotrexate	4
Bleomycin	7
Doxorubicin	3
Vincristine	2
Etoposide	2
All PACEBOM	2
GCSF support on PACEBOM	
Yes	7 (19)
No	30 (81)
Red Blood Cell transfusion on PACEBOM	
Yes	19 (51)
No	18 (49)
Platelet transfusion	
Yes	7 (19)
No	30 (81)

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