The anglia regional experience of using PEP-C as palliative chemotherapy in relapsed refractory lymphoma: A multicentre retrospective cohort study.

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Abstract

PEP-C (Prednisolone, Etoposide, Procarbazine, and Cyclophosphamide) is an orally administered daily chemotherapy regimen used with palliative intent in relapsed refractory lymphoma. To our knowledge no data on PEP-C has been reported since the original group described the regimen. Here we present a multicentre retrospective cohort reporting our use of PEP-C in 92 patients over an eight-year period. We find that even heavily pretreated lymphoma can respond to PEP-C, particularly low grade lymphoma (including mantle cell) and lymphoma that was sensitive to the previous line of systemic therapy (chemosensitive). These characteristics may help in the selection of patients likely to derive benefit. The median overall survival of patients with chemosensitive lymphoma treated with PEP-C is 217 days. Within the limitations of a retrospective cohort we find that PEP-C is well tolerated: The most common toxicity leading to discontinuation is marrow suppression. We suggest that PEP-C should be considered for patients with relapsed refractory lymphoma in two settings: Firstly, where there is no licensed alternative; and secondly, where the licensed alternative is an intravenous drug and the burden of frequent hospital visits for intravenous drug administration would be too great.

Keywords: Lymphoma, Prednisolone, Intraventricular haemorrhage, Procarbazine, Cyclophosphamide.

Introduction

The choice of therapy in the setting of relapsed/refractory lymphoma is dependent upon lymphoma subtype, previous treatment received, disease response, and individual patient factors. In high grade Non-Hodgkin Lymphoma (NHL) such as Diffuse Large B-Cell Lymphoma (DLBCL) some patients will benefit from intensive salvage chemotherapy with regimens such as R-DHAP (Rituximab, Dexamethasone, Cytarabine, Cisplatin) or R-ICE (Rituximab, Ifosfamide, Carboplatin, Etoposide) followed by stem cell transplantation for those who respond.Similarly some patients with Mantle Cell Lymphoma (MCL) or low grade NHL such as Follicular Lymphoma (FL) will benefit from intensive chemotherapy with or without stem cell transplant. There are many patients, however, who have either responded inadequately to these regimens or whose performance status or co- morbidities preclude their use. These patients have a poor prognosis but may benefit from palliative chemotherapy in order to prolong life and/or provide relief from disease related symptoms. Given the palliative intent of such therapy, quality of life and tolerability of treatment are crucial considerations in the decision making for these patients [1].

There is no general consensus on the optimum regimen although there are now some licensed options: Pixantrone is licensed for the treatment of multiply relapsed or refractory aggressive B-cell NHL in adults; and ibrutinib has a licence for the treatment of relapsed or refractory MCL in adults. PEP-C is a palliative chemotherapy regimen previously reported as being used in the relapsed/refractory setting for both mantle cell and other of lymphoma. Its main advantage for use in this setting is that it is oral therapy that can be given on an outpatient basis [2]. To our knowledge no data has been published regarding this regimen since the initial reports of the Weill Cornell/New York Presbyterian group. We have been using PEP-C for relapsed/refractory lymphoma since these reports, and here we present a multicentre retrospective cohort describing our experience of PEP-C over the past eight years. The objective of this study is to examine the efficacy and tolerability of PEP-C.

Materials and Methods

Patients

PEP-C was introduced into the Anglia region of England in February 2009. All patients who received PEP-C across five centres were identified from pharmacy records and followed up by means of their patient records [3]. For the purposes of survival analysis patients who continued on PEP-C or who

were still alive at the time of the study were censored on 24th March 2017.

PEP-C treatment protocol

In three of the five treatment centres treatment was administered essentially as described by. Patients received prednisolone 20 mg after breakfast, cyclophosphamide 50 mg after lunch, etoposide 50 mg after evening meal, and procarbazine 50 mg at bedtime. Treatment was divided into three phases: Firstly, there was an induction phase where PEP-C was given daily until the white cell count fell to below 3.0 × 109 /L; secondly, upon induction of marrow suppression, there was a break where treatment was withheld until white cell count recovery to above 3.0 × 109 /L; and thirdly, there was an maintenance phase where patients were re-started on PEP-C on three days of the week (usually Mondays, Wednesdays, and Fridays). The number of days of the week on which PEP-C was administered in the maintenance phase was titrated as required to maintain a white cell count greater than 3.0 × 109 /L. During the induction phase of treatment for a full blood count was assayed weekly. Thereafter the frequency of blood count monitoring was based upon clinical judgement. In two out of the five treatment centres alternative regimens were used: In one centre daily treatment with PEP-C was administered for 14 days on and 14 days off; in the other treatment was administered for 10 days on and 18 days off [4].

Evaluation of response to PEP-C

As far as possible the international harmonization project revised response criteria for malignant lymphoma were followed. As patients were in a palliative phase of their treatment, however, and as they were not being treated as part of a clinical trial the re-assessment of disease status was not usually as intense as it might otherwise have been. In particular the use of Positron Emission Tomography (PET) and bone marrow biopsy to assess response was rare. Sometimes patients with palpable disease were managed based upon clinical assessment without further imaging. In light of this we allowed a patient to be designated as having made a complete response to treatment if no detectable disease remained on Computed Tomography (CT) scanning and we did not mandate a negative bone marrow biopsy.

If a patient with palpable disease was documented to have clinically convincing regression of masses we allowed this as a partial response. If a patient had an objective assessment of response to PEP-C and did not achieve a complete or partial response we designated this disease 'refractory' to PEP-C as differentiating stable from progressive disease was in many cases impossible based upon the information available [5].

Statistical analysis

Our statistical analyses consist of data from patients who received any amount of PEP-C. We used Stata/IC version 14. The statistical tests employed are given with the corresponding results [6,7].

Results

Patient characteristics and details of PEP-C treatment

Ninety six patients were identified from pharmacy records as having been prescribed PEP-C from February 2009 (the date of introduction of PEP-C to the Anglia region of England) to March 2017. Ninety two of these patients are known to have received PEP-C, two having died before PEP-C was started and two having no records available. The censoring date for survival analysis was 24th March 2017. Within this period of follow-up 82 patients finished treatment with PEP-C and 70 patients died. Patient characteristics at the time of the initial lymphoma diagnosis are shown in supplementary [8]. The median age was 69 years and 60% of the patients were male. 48% of the patients had an International Prognostic Index (IPI) of three or greater. The median number of lines of systemic treatment given prior to PEP-C was 2, and the median number of complete or partial responses to treatment prior to PEP-C was 1 [9].

11% of the patients received a peripheral blood stem cell or bone marrow transplant prior to receiving PEP-C. In assessing the response a patient made to his most recent chemotherapy prior to PEP-C the disease is classed as 'refractory' if neither a partial nor complete response was achieved. Under this system 36% of patients were refractory to their most recent line of chemotherapy prior to PEP-C. From here on in if a patient had a complete or partial response to his most recent line of systemic therapy prior to PEP-C we designate that patient 'chemosensitive'; and if a patient was refractory to his most recent line of chemotherapy prior to PEP-C we designate that patient 'chemoresistant'. The histological subtypes of lymphoma included in our cohort are shown [10]. If a patient's histological diagnosis changed over time (e.g. DLBCL transformed from FL) the histological diagnosis at the time of starting treatment with PEP-C. Thirty two percent of patients had DLBCL, and another 26% had other forms of high grade B-cell NHL. This 26% consisted of DLBCL transformed from FL (9 patients), DLBCL transformed from low grade lymphoma (8 patients), grade 3 FL (2 patients), Burkitt lymphoma (3 patients), and high grade B-cell NHL not otherwise specified (2 patients). Twenty five percent of patients had mantle cell lymphoma, and 8% had low grade B-cell NHL consisting of Chronic Lymphocytic Leukaemia (CLL, 2 patients), Small Lymphocytic Lymphoma (SLL, 1 patient), grade 1 or 2 FL (1 patient), lymphoplasmacytic lymphoma (1 patient), and low grade B-cell NHL not otherwise specified (2 patients). Small numbers of patients had T-cell lymphoma and classical Hodgkin's disease [11,12].

One patient had a myeloid malignancy. At the time of commencing treatment with PEP-C the median patient age was 73 years. Ninety one percent of patients had stage 3 or 4 disease, 38% had more than one extranodal site of disease, and 24% had a performance status of 3 or 4 although note that the performance status data when starting PEP-C was missing for 27% of the cohort. Typically patients had 21 days of induction

treatment with PEP-C. Where patients did have a break from induction treatment before starting maintenance this was typically a 7 day break but many patients, having not achieved myelosuppression with three weeks of induction treatment, moved from induction straight into maintenance. This is why the median treatment break prior to starting maintenance is calculated as zero days. Maintenance treatment was most commonly given on three days out of every week (usually Mondays, Wednesdays, and Fridays). There was, however, considerable variation in dose requirement in the maintenance phase with one patient tolerating maintenance treatment every day of the week and one patient taking PEP-C on one day one week and two days the next [13]. As set out for an above, two of the centres in this study used a different PEP-C regimen from the others. These two centres accounted for 19 out of the 92 patients. In none of the analyses presented below was there a significant effect of treatment centre on the reported outcomes so the data has been pooled **(Table 1).**

Table 1. *Patient characteristics when starting treatment with PEP-C and details of PEP-C treatment.*

Patient characteristics when starting PEP-C and details of PEP- C treatment	
Patient characteristics when starting PEP-C and details of PEP-C treatment	**n=92**
Median age, years (IQR) (range)	73 (67 to 80) (30 to 90)
Lymphoma subtypes	
DLBCL	29 (32%)
Other high grade B-cell NHL	24 (26%)
Mantle cell lymphoma	23 (25%)
Low grade B-cell NHL	7 (8%)
T-cell lymphoma	5 (5%)
Classical Hodgkin's disease	3 (3%)
Myeloid malignancy	1 (1%)
ECOG performance status	
0-2	45 (49%)
44654	22 (24%)
Missing	25 (27%)
Ann-Arbor stage	
44593	8 (9%)
44654	84 (91%)
0-1	57 (62%)
>1	35 (38%)
Median duration of disease from initial diagnosis, months (IQR)	28 (14 to 64)
Median length, days of PEP-C induction treatment (IQR)	21 (14 to 29)
Median length, days of break from PEP-C before starting maintenance (IQR)	0 (0 to 8)
Median maintenance dose, days per week of PEP-C (IQR)	3 (3 to 3.5)
Median duration of treatment, days with PEP-C (IQR)	76 (28 to 159)
Reason PEP-C discontinued	See figure 1
Toxicities	n=59 patients, 113 toxicities
Uncomplicated marrow suppression	21 (18%)
Neutropenic sepsis	10 (9%)
Viral reactivation	3 (3%)
Other infections	31 (27%)
Gastrointestinal	21 (18%)
Fatigue	7 (6%)
Respiratory	4 (4%)
Cardiac	2 (2%)
Hair loss	2 (2%)
Bleeding	2 (2%)
Other	10 (9%)

Response to PEP-C

Of the 92 patients treated with PEP-C ten achieved a Complete Response (CR) and 29 achieved a Partial Response (PR). Forty patients did not achieve a CR or PR and were considered to have disease 'refractory' to PEP-C (either stable disease or progressive disease). Given that a group size of ten for CR is not practicable for statistical analysis we categorized patients as having responded to PEP-C (CR or PR) or as having being refractory to PEP-C (stable disease or progressive Disease). In 13 cases there was no suitably objective assessment of the response to PEP-C to allow us to categorize the response. Similarly, some histological subtypes of lymphoma did not contain sufficient patient numbers to allow for meaningful statistical analysis. We therefore grouped lymphoma subtype into low grade versus high grade. The low grade lymphoma group consists of mantle cell lymphoma (23 patients), 'low grade B-cell NHL' (7 patients), and the myeloid malignancy. The low grade lymphoma group is therefore dominated by mantle cell lymphoma. Ideally mantle cell lymphoma were that would have been considered separately but the survival curves for the groups that were combined were similar (not shown) and we do not believe that combining the groups made any meaningful difference to our results or masked detail that would otherwise have been apparent. The high grade lymphoma group consists of all the other histological subtypes and contains 61 patients in total. The major constituent of this group is the 46 patients with DLBCL either de novo or transformed. Overall 39 out of 92 patients (42%) responded to PEP-C whilst 40 (43%) were refractory. In the remaining patients there was no suitably objective measure of response to allow categorization.

Built by backwards elimination. The significant predictors in the multivariate model were: Whether a patient had low or high grade disease; whether or not a patient had responded to the line of chemotherapy prior to PEP-C (chemosensitive versus

chemoresistant); and whether or not a patient had extranodal disease when starting treatment with PEP-C. Nineteen out of 31 patients (61%) with low grade disease responded to PEP-C compared to 20 out of 61 patients (33%) with high grade disease. Compared to patients with high grade lymphoma, patients with low grade lymphoma had reduced odds of being refractory to PEP-C (odds ratio=0.17 (95% CI 0.05 to 0.60); p=0.006). Similarly, 25 out of 50 patients (50%) with chemosensitive disease responded to PEP-C whilst only nine out of 33 patients (27%) with chemoresistant disease responded to PEP-C. Compared to patients who were chemoresistant, patients who were chemosensitive had reduced odds of being refractory to PEP-C (odds ratio=0.27 (95% CI 0.08 to 0.91); p=0.035). Twenty three out of 68 patients (34%) with extranodal disease when they started PEP-C responded to treatment, compared to 16 out of 24 patients (67%) who were free of extranodal disease **(Table 2).**

Table 2. *Response to PEP-C for all patients and subdivided by patient characteristics.*

Patient characteristic	CR or PR to PEP-C	Refractory to PEP-C	Response to PEP-C not assessed	Total
Lymphoma				
Low grade	19	9	3	31
High grade	20	31	10	61
Response to previous line of chemotherapy				
CR or PR (chemosensitive)	25	19	6	50
Refractory (chemoresistant)	9	17	7	33
Missing data	5	4	0	9
No extranodal disease	16	6	2	24
Extranodal disease	23	34	11	68
Total	39	40	13	92

Compared to patients without extranodal involvement, patients with extranodal involvement have increased odds of being refractory to PEP-C (odds ratio 7.4 (95% CI 2.0 to 27.6); (p=0.003). There was no significant interaction between any of the three independent variables in the logistic regression model (not shown). We have not provided an analysis broken down into the eight groups that could be created from three independent variables (low grade and chemosensitive and without extranodal involvement; low grade and chemosensitive and with extranodal involvement; and so on) as the numbers in the groups become too small to be meaningful. As patients often ask for some idea of their prognosis depending on whether they respond to a treatment we have provided an analysis. We have placed a landmark at 28 days in the survival analysis to compensate for immortal time bias. Patients who were refractory to PEP-C had a median overall survival of 78 days versus 418 days in responding patients (hazard ratio 4.18 (95% CI 2.30 to 7.61); log rank p<0.0001). The proportional hazards assumption was found to be valid based upon the Schoenfeld residuals test.

Overall survival from starting treatment with PEP-C

For the entire cohort the median overall survival from starting treatment with PEP-C was 163 days (95% CI 95 to 230). Using univariate COX proportional hazards regression for continuous variables and the log rank test of equality across strata for categorical variables, possible predictors of overall survival were tested. A multivariate COX proportional hazards regression model was then built by backwards elimination. Although we have already shown that the response to PEP-C is a significant predictor of overall survival in a landmark analysis we did not include this in our model as it is not a variable that can be used a priori to help make a judgement about whether a patient might benefit from treatment. The significant predictors of overall survival were found to be: Whether a patient had high or low grade lymphoma; whether a patient had responded to the last line of chemotherapy prior to PEP-C (chemosensitive *versus* chemoresistant).

Whether a patient had stage 4 disease versus non-stage 4 disease when starting treatment with PEP-C. Median overall survival with low grade lymphoma was 409 days versus 100 days with high grade lymphoma (hazard ratio=0.35 [95% CI 0.19 to 0.63]; p<0.001). Note, however, that the estimate of median survival for patients with low grade lymhpoma is based upon very few failures at the critical time and so the confidence interval around this value is wide. For chemosensitive patients the median overall survival was 217 days versus 100 days for chemoresistant patients (hazard ratio=0.36 (95% CI 0.21 to 0.62); p<0.001). For patients with stage 4 disease the median overall survival was 100 days (95% CI 78 to 163) compared to 252 days (95% CI 163 to 535) in patients with non-stage 4 disease (hazard ratio 2.2 (95% CI 1.2 to 3.8); p=0.007). This multivariate model was made to interact with the logarithm of time as a time varying covariate and the proportional hazards assumption was found to be valid (Figures 1-4).

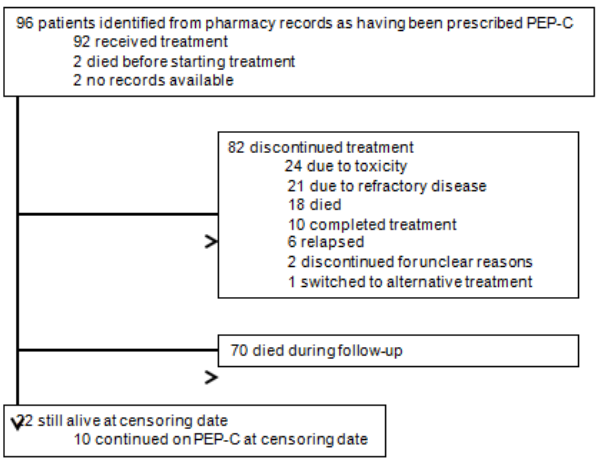

Figure 1. *Study profile.*

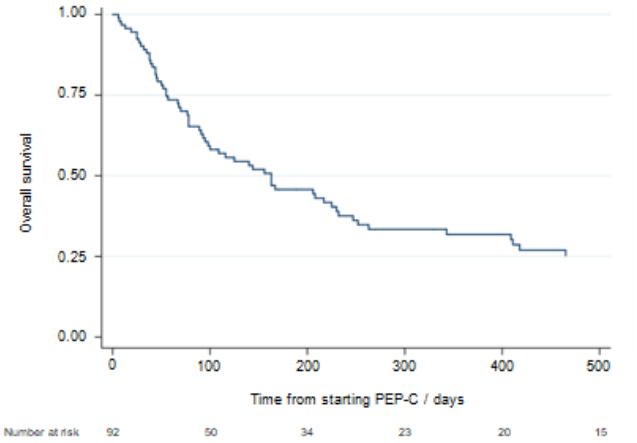

Figure 2. *Kaplan-Meier survival estimate of overall survival from starting treatment with PEP-C.*

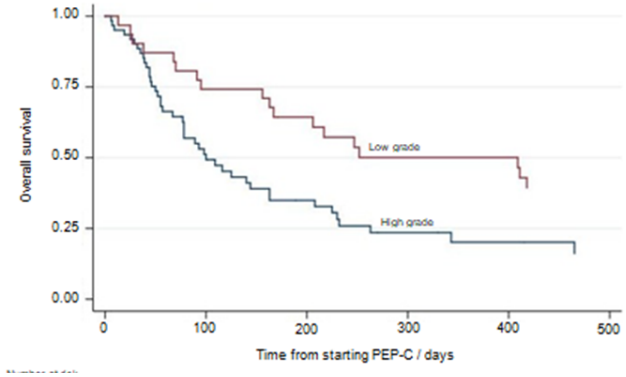

Figure 3. *Kaplan-Meier survival estimates of overall survival from starting treatment with PEP-C.*

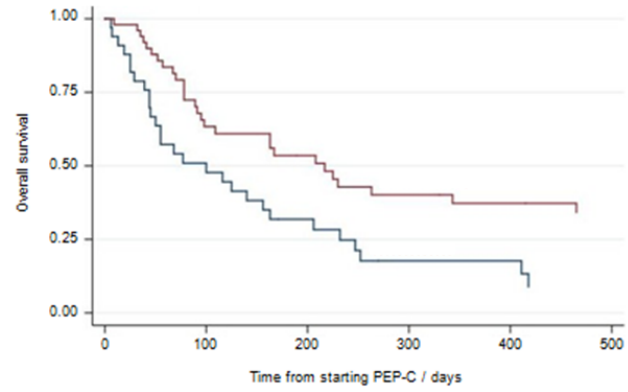

Figure 4. *Kaplan-Meier survival estimates of overall survival from starting treatment with PEP-C.*

Toxicities and cost

Twenty four patients (29%) discontinued PEP-C due to toxicity. Ten of these were uncomplicated marrow suppression (i.e. low counts but with no bleeding or infection), whilst six were due to neutropenic sepsis, and five due to non-neutropenic sepsis. The remaining three toxicities were one case each of fungal pneumonia (therefore also related to immunosuppression), nausea, and a transient ischaemic attack. The notes of 59 patients were available for more detailed assessment of toxicities and the results are summarized. The three viral reactivations were two cases of shingles and one case of herpes simplex reactivation as a cold sore. The 'other infections' were primarily respiratory tract infections that were either not in the context of neutropenia or not severe enough to warrant hospital admission for intravenous therapy. The gastrointestinal side effects predominantly consisted of ten cases of nausea, three cases of dysphagia, and 2 cases of oral ulcers of unclear aetiology although it must be a strong possibility that these ulcers were viral. The 'other' toxicities predominantly include adverse events unlikely to be directly related to PEP-C such as right leg weakness, peripheral oedema, disorientation, neuropathy, arthralgia, and a transient ischaemic attack. Based upon figures from the British National Formulary of National Health Service (NHS) pricing, a 28 day cycle of PEP-C would cost £ 390.37 if PEP-C were to be taken daily for 28 days. If the 'median' patient from our cohort is considered, who is on induction treatment for 21 days and then goes onto maintenance treatment for three days. Every week for the remainder of the 76 day total treatment duration, the cost of the drugs for the entire course would be £ 557.67.

Discussion

In this study we have presented a multicentre retrospective cohort of 92 patients treated with PEP-C for relapsed/refractory lymphoma. Our study therefore suffers from the usual limitations of a single-group cohort. As the cohort is retrospective there is also significant missing data in some areas (e.g. performance status when starting PEP-C. Other high grade B-cell NHL' consists of DLBCL transformed from FL (9 patients), DLBCL transformed from low grade lymphoma (8 patients), grade 3 FL (2 patients), Burkitt lymphoma (3 patients), and high grade B-cell NHL not otherwise specified (2 patients). 'Low grade B-cell NHL' consists of CLL (2 patients), low grade B-cell NHL not otherwise specified (2 patients), SLL (1 patient), grade 1 or 2 FL (1 patient), and lymphoplasmacytic lymphoma (1 patient). 'T-cell lymphoma' consists of peripheral T-cell lymphoma (4 patients) and anaplastic large cell lymphoma (1 patient). The 113 toxicities of PEP-C treatment listed are taken from a review of all the clinic letters of 59 patients whose records were available for more detailed scrutiny. The viral reactivations consist of 2 cases of shingles and 1 cold sore. The 31 cases of 'other infections' consist largely of suspected respiratory tract infections in non-neutropenic patients. Of the 21 cases of gastrointestinal side effects ten were nausea. The 'other' side effects are diverse groups including leg weakness, disorientation, nocturia, urinary retention, a transient ischaemic attack. Diffuse Large Cell B-cell Lymphoma (DLBCL), Non-Hodgkin's Lymphoma (NHL), Follicular Lymphoma (FL), Chronic Lymphocytic Leukaemia (CLL), Small Lymphocytic Lymphoma (SLL).

Response to PEP-C for all patients and subdivided by patient characteristics found to be statistically significant in a multivariate logistic regression model. A patient is considered to be 'refractory' to PEP-C or to his previous line of

chemotherapy ('chemoresistant') if a CR or PR has not been achieved and the response has been satisfactorily assessed. 'Previous line of chemotherapy' refers to the most recent course of systemic treatment given to the patient prior to PEP-C. The presence or absence of extranodal disease refers to disease status when starting treatment with PEP-C rather than to disease status at in the initial diagnosis. Complete Response (CR), Partial Response (PR). We found to be in the statistically significant in a multivariate logistic regression model. A patient is considered to be 'refractory' to PEP-C or to his previous line of chemotherapy ('chemoresistant') if a CR or PR has not been achieved and the response has been satisfactorily assessed. 'Previous line of chemotherapy' refers to the most recent course of systemic treatment given to the patient prior to PEP-C. The presence or absence of extranodal disease refers to disease status when starting treatment with PEP-C rather than to disease status at the initial diagnosis. (CR) Complete Response, (PR) Partial Response. Do not, however, believe that these limitations mean that useful conclusions cannot be drawn. When starting treatment with PEP-C the median age in our cohort was 73 years, and almost a quarter of patients had a performance status of three or four.

Our cohort was therefore relatively frail and many of our patients would have been excluded from prospective trials for newer drugs licensed in this setting e.g. pixantrone. In our study we found that there were two significant predictors of a patient both responding to PEP-C and having improved overall survival. These were low grade disease (mainly mantle cell lymphoma) as opposed to high grade disease (mainly de novo or transformed DLBCL) and a patient having made a response to their previous line of chemotherapy (chemosensitive) compared to not having done so (chemoresistant). Therefore in considering whether a patient might benefit from treatment with PEP-C these factors may be useful to take into consideration. A note of caution is that seven chemoresistant patients did not have an adequate assessment of response to PEP-C and so do not appear in these numbers. These seven patients, however, had overall survivals from starting PEP-C of (45, 68, 116, 125, 140, 163, and 247) days. It may be that some of these patients did respond to PEP-C but never had the response formally assessed due to the palliative phase of their care with management being based upon symptomatology. When a patient does respond to PEP-C the benefits can apparently be sustained and patients who did respond to PEP-C had a median overall survival of 418 days (13.8 months) from the time of commencing treatment with PEP-C in a landmark analysis.

Survival estimates grouped by the response a patient made to the line of systemic treatment prior to PEP-C. X-axis truncated at 500 days. Patients who were chemosensitive had a median overall survival of the 217 days (95% CI 98 to 465) *versus* 100 days (95% CI 45 to 163) for patients who were chemoresistant. Hazard ratio=0.36 [95% CI 0.21 to 0.62]; p<0.001. Survival estimates grouped by histological diagnosis. X-axis truncated at 500 days. Patients with low grade disease had a median overall survival of the 409 days (95% CI 163 to 599) *versus* 100 days (95% CI 77 to 163) for patients with high grade disease. Hazard ratio=0.35 [95% CI 0.19 to 0.63]; p<0.001. The predictors of survival (low *versus* high grade lymphoma, and whether or not a patient had responded to their most recent line of chemotherapy prior to those PEP-C (chemosensitive *versus* chemoresistant)) were both found to conform to the proportional hazards assumption and they did not interact significantly. The statistics quoted are from a multivariate cox proportional hazards regression model. Overall 39 out of 92 patients (42%) in our study responded to PEP-C. Of those with high grade lymphoma 20 out of 61 (33%) had a response. Reported ten out of 23 (43%) patients with high grade lymphoma to have had a complete or partial response to PEP-C so our findings bear out theirs in as much as we find that a significant proportion of patients with high grade disease can respond to PEP-C.

The situation is similar for other types of lymphoma. Of patients we classified as having low grade lymphoma (a group consisting mainly of mantle cell lymphoma) 19 out of 31 (61%) responded to PEP-C. A response rate to PEP-C of 82% (18 out of 22) in mantle cell lymphoma and a response rate of 79% (41 out of 52) in a combination of. FL, SLL, and marginal zone lymphoma. We therefore agree that a significant proportion of patients with low grade disease may benefit from treatment with PEP-C. In our study 24 out of 82 patients (29%) discontinued PEP-C due to toxicity, and toxicity was the single biggest reason for PEP-C being stopped. Almost all of these toxicities were marrow suppression with or without complications, but this is perhaps not unexpected. When considering the number of patients for whom toxicity led to the cessation of PEP-C it is important to bear in mind that patients were being treated palliatively so physicians may have been readier to stop treatment to avoid recurrent toxicity than otherwise might have been the case. The toxicities reported with PEP-C that caused patients symptomatic distress such as nausea appear to have been manageable as only one patient stopped treatment with PEP-C due to these symptoms. It is important to recognise, however, that in a retrospective study such as this outside the context of a clinical trial we will almost certainly not have detected many of the toxicities that would have been reported in a trial setting.

Conclusion

In conclusion we suggest that PEP-C can be an efficacious, well tolerated, and inexpensive chemotherapy regimen for relapsed/refractory lymphoma. It benefits from being an oral regimen that can be delivered on an outpatient basis. We suggest that PEP-C should be considered for patients with relapsed/refractory lymphoma in two settings: Firstly, where there is no licensed alternative; and secondly, where the licensed alternative is an intravenous drug and the burden of frequent hospital visits for intravenous drug administration would be too great.

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