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Single arm phase II trial assessing the safety, compliance with and activity of Bezafibrate and medroxyProgesterone acetate (BaP) therapy against myeloid and lymphoid cancers

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ABSTRACT

We previously reported the safety and efficacy of low dose BaP [**B**ezafibrate (Bez) **a**nd Medroxy**p**rogesterone acetate (MPA)] in 20 acute myeloid leukaemia (AML) patients for whom chemotherapy was not an option. This study provided evidence that BaP had anti-AML activity and improved haemopoiesis; absence of haematological toxicity allowed continuous daily administration. Similarly a previous trial in endemic Burkitt lymphoma demonstrated anti-B cell lymphoma activity of low and high dose BaP again in the absence of toxicity.

We conducted a study to further evaluate the safety and activity of high dose BaP therapy in adults with AML (and high risk Myelodysplastic Syndromes (MDS)), chronic lymphocytic leukaemia (CLL) or B-cell Non-Hodgkin Lymphoma (BHNL). Eighteen patients were recruited to the study over 20 months, 16 AML/MDS, 1 CLL, and 1 BNHL. Although MPA was well tolerated throughout the study, only 2 patients were able to tolerate Bez treatment for their whole trial duration, indicating that Bez escalation is not feasible in the setting of adult AML/MDS. Thus there has been no obvious benefit in improved haemopoiesis or overt anti-leukaemia activity from the attempts to escalate BaP dose over previous published studies. Since current therapeutic options in MDS are restricted it may be now of value to continue to evaluate low dose BaP based approaches in low risk MDS rather than AML/high risk MDS. Furthermore, screening of low dose BaP against libraries of other already available dugs may identify an addition to BaP that augments the anti-neoplastic efficacy without significant toxicity.

1. Introduction

1.1. More than half of all patients with Acute Myeloid leukaemia (AML) and substantial proportions of

Chronic Lymphocytic Leukaemia (CLL) and B-cell Non-Hodgkins Lymphoma (BNHL) patients either present, or reach a point in their disease, where anti-cancer therapy is inappropriate because it is no longer effective or its toxicity cannot be tolerated, usually due to age and infirmity. At this stage of their disease the loss of normal haemopoiesis creates life-threatening deficits of erythrocytes, platelets, and neutrophils that are managed using blood and platelet transfusion and aggressive treatment of neutropenic infections. Other than palliative treatment with prednisolone in B cell malignancy and hydroxyurea to control rising myeloid blast counts, there is no available treatment and survival is poor.

We previously reported the safety and efficacy of low dose BaP [**B**ezafibrate (Bez) **a**nd Medroxy**p**rogesterone acetate (MPA)] in 20 AML patients for whom chemotherapy was not an option (ISRCTN50635541) [1]. The study provided evidence of both anti-AML activity and improved haemopoiesis; absence of haematological toxicity allowed continuous daily administration.

Subsequent in vitro studies indicated that Bez doses 12x and MPA doses 2.5x that used in the above study (termed hereafter as full dose

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Table 1
Patient Characteristics (n = 16 unless stated otherwise).

Median (IQR) age (years)	75.3 (67.9–77.8)
Sex	
Male	11 (68.7%)
Female	5 (31.3%)
ECOG performance status	
0	4 (25.0%)
1	7 (43.7%)
2	2 (12.5%)
3	2 (12.5%)
Missing	1
Diagnosis	
MDS (RAEB2)	2 (12.5%)
AML transformed from MDS	5 (31.3%)
Other secondary AML	1 (6.3%)
Primary AML	7 (43.8%)
Missing	1
Median (IQR) time from original diagnosis to trial entry (weeks)	13.3 (3.6–75.0)
Missing	1
Disease status	
Previously untreated	8 (50.0%)
Relapsed	5 (31.3%)
Refractory	2 (12.5%)
Missing	1
Transfusion dependent (TD) patients	
Red blood cell	9 (56.3%)
Platelet	4 (25.0%)
Missing	1
Haemoglobin in patients that are not red blood cell TD	(n = 6)
Median (IQR) Haemoglobin (g/dL)	10.4 (9.4–12.0)
Platelets in patients that are not platelet TD	(n = 11)
$> 100 \times 10^9$/L	4 (36.4%)
20–100 $\times 10^9$/L	5 (45.4%)
$< 20 \times 10^9$/L	2 (18.2%)
Median counts (IQR)	
White cell count (x10^9/L)	2.2 (1.4–7.0)
Missing	1
Neutrophils (x10^9/L)	
$\geq 1 \times 10^9$/L	4 (25.0%)
$< 1 \times 10^9$/L	10 (62.5%)
Not known	1 (6.3%)
Missing	1

BaP), would likely have substantially greater efficacy against AML [2]. We have also reported the safety and efficacy of BaP in primary resistant and relapsed Burkitt lymphoma in Malawi (ISRCTN34303497). 33 children received low dose BaP, 28 intermediate dose and 34 full dose without evidence of toxicity, and with evidence of anti-lymphoma activity most effective at the full dose [3].

This current study was therefore designed to further evaluate the safety, compliance (feasibility of delivery) and activity of full-dose BaP in adults with AML (and high risk MDS), CLL or BNHL.

2. Methods

Enrolment of patients took place between October 2012 and June 2014. As this was a pilot study, it did not involve any formal statistical hypothesis testing. Whilst anticipating recruiting 20 patients to each of the 3 diseases, the trial was terminated at a total of 18 patients (16 with AML/MDS (RAEB2) and 1 each of CLL and BNHL) due to slow recruitment and time spent amending the protocol dosing. Patient characteristics of the AML/MDS (RAEB2) cohort are given in Table 1.

The initial protocols used for this study were a starting dose of Bez (modified release) of 2400 mg twice daily in patients with an eGFR $\geq$60 ml/min. Where patients had an eGFR of 40–59.9 ml/min, the starting dose of Bez (standard release) was 1200 mg twice daily. All patients received 1000 mg MPA daily. All analyses were descriptive, with no statistical testing.

Outcomes: safety, compliance, haematological response and survival [4].

3. Results

3.1. AML/MDS (RAEB 2) cohort

MPA was well tolerated throughout the study with 9/16 patients taking MPA continuously throughout the trial. 14/16 patients took MPA for more than 80% of the trial duration. One of the 16 patients did not start treatment due to poor health. There were no occasions where the patient stopped MPA but not Bez, although patients frequently took MPA alone.

Of the four patients recruited to the initial protocols, three patients took the full dose of modified release Bez (4800 mg daily) but none for more than two weeks. The fourth patient commenced on standard release Bez at the full dose (2400 mg daily) but discontinued after 5.9 weeks. The protocol was subsequently amended to reduce the starting dose to 1600 mg daily of modified release Bez or 800 mg daily standard release Bez, with the ability to dose escalate up to 4800 mg daily of modified release Bez or 2400 mg daily standard release Bez.

12 patients were recruited onto this amended protocol; of those that had more than four weeks of treatment, four had a mode dose of 1600 mg and one had a mode dose of 3200 mg (the mode dose was taken in these patients for a range of 3–7 weeks). Only 2 patients on the amended protocol were able to take Bez for their whole trial duration which was 5.4 weeks for one patient and 8.6 weeks for another. All other patients had at least one period where their Bez had to be interrupted. No patient was able to escalate to the full dose of BaP therapy.

Interruptions or changes in Bez doses were largely due to either a rise in Creatinine Kinase (CK) or a fall in eGFR. In one patient receiving 4800 mg daily of Bez, treatment had to be stopped because of myalgia and an elevated CK indicative of rhabdomyolysis. In a further five patients, Bez was temporarily stopped because of elevations of CK (in two patients associated with myalgia and one with oedema); all patients recommenced lower doses of Bez. All patients experienced their first rise in CK within two weeks of starting modified release Bez at a dose of 1600 mg.

Bez is contraindicated in patients with an eGFR $<$ 40 ml/min and if the eGFR drops below 60 ml/min, patients must change from modified Bez to standard release Bez. In six patients (10 occasions), reductions in eGFR required a change in the dose of Bez and in five of these patients (7 occasions) this also required a change in formulation.

Compliance was assessed using patient diaries against dose prescribed. Where a patient diary was unavailable it was assumed that the patient was non-compliant for the duration of the missing diary. The median (IQR) compliance for Bez for all patients was 75% (68–96) and 75% (70–91) for MPA. The median (IQR) compliance for Bez for patients with all patient diaries returned was 95% (79–100) and 94% (84–100) for MPA. The most common reasons for non-compliance were difficulty in taking the large number of tablets required to deliver the full dose, hospital admissions and nausea.

Toxicities were also reported at higher grades and rates than in previous BaP studies [1,3] with 12 and 6 occurrences of grade 3 and 4 toxicities respectively assessed as being at least possibly related to BaP. The majority of these events fell into the 'Investigations' category. The median survival for this cohort of patients was 10.6 weeks (95% CI: 6.6, 20.6).

Seven patients took trial medication for $>$ 8 weeks and three

for > 12 weeks; one had a haematological response (erythroid and platelets). Median survival was 10.6 weeks (95% CI: 6.6, 20.6).

3.2. CLL and BNHL cohorts

Only 1 patient was recruited into each of these cohorts. The BNHL patient (male, 71.9 years, ECOG = 0, relapsed disease) received 5 weeks of standard release Bez and 4.9 weeks of modified release Bez, MPA was continued throughout. BaP was discontinued at 18 weeks due to disease progression. The CLL patient (male, 81.4 years, ECOG = 1, relapsed disease) withdrew from the trial after 5 days due to toxicity. The time from registration to death for the BNHL patient was 28.0 weeks and 27.7 weeks for the CLL patient.

4. Discussion

Although high dose BaP was tolerated and efficacious in children with endemic Burkett's lymphoma [3], this elderly patient group have not tolerated high dose Bez. This intolerance reflects multiple reasons including reduced and fluctuating renal function and a propensity to develop myalgia with elevated CK. Therefore, future trials should consider only recruiting patients with an eGFR greater than 50 ml/min and using only the standard release formulation of Bez to improve duration of treatment.

Whilst difficult to draw conclusions from this study due to the challenges in patients remaining on treatment with Bez, there has been no obvious benefit in improved haemopoiesis or overt anti-leukaemia activity from the attempts to escalate BaP dose over the previous published study [1]. No conclusions about the efficacy or safety of BaP in CLL or BNHL can be drawn due to only 1 patient being recruited in each cohort. BaP therapy is not a competitive option in CLL at this time given the new drugs that have recently become available to these patients [5]. Generically BaP is not attractive in BNHL at this time. However, given the efficacy seen in children with endemic Burkitt's lymphoma [3] and the lack of effective regimens for relapsed and refractory sporadic Burkett's lymphoma there is cause to consider a pilot study in this setting.

Since starting the BaP trial, a number of competing trials have developed in the AML setting in the UK. Due to this and the results of this present study, it would appear that BaP based approaches in AML are not currently viable. A further common challenge that has faced the two BaP trials in AML has been the immediate poor prospects of the patients entering the trials with most expected to deteriorate over the first few weeks. Despite this, the first trial of low dose BaP saw significant haematological response in 4/11 evaluable patients for 22, 29, 30 and 201 weeks and no deterioration in haemopoiesis in the other 8 whilst on BaP therapy. However, these effects took greater than four weeks to arise during which time many patients disease progressed significantly. Since the current therapeutic options in MDS are restricted it may be of value to continue to evaluate a BaP based approach in this setting rather than AML. Furthermore, screening of low dose BaP against libraries of other already available dugs may identify a more efficacious combination with increased anti-neoplastic effect and little or no increased toxicity.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2019.100361.

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