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A phase II trial of bryostatin 1 in patients with non-Hodgkin's lymphoma

FH Blackhall[1], M Ranson[1], JA Radford[1], BW Hancock[2], M Soukop[3], AT McGown[4], A Robbins[5], G Halbert[6] and GC Jayson[1] for the Cancer Research Campaign Phase I/II Committee

[1]CRC Department of Medical Oncology, Christie Hospital NHS Trust, Wilmslow Road, Withington, Manchester; [2]YCRC Department of Clinical Oncology, Weston Park Hospital NHS Trust, Whitham Road, Sheffield; [3]Department of Medical Oncology, Royal Infirmary, 84 Castle Street, Glasgow; [4]CRC Drug Development Group, Paterson Institute for Cancer Research, Wilmslow Road, Withington, Manchester; [5]Drug Development Office, Cancer Research Campaign, 10 Cambridge Terrace, London; [6]CRC Formulation Unit, Department of Pharmaceutical Sciences, University of Strathclyde, Royal College Building, 204 George Street, Glasgow, UK

Summary Bryostatin 1 is a naturally occurring macrocyclic lactone with promising antitumour and immunomodulatory function in preclinical and phase I clinical investigations. In this phase II study, 17 patients with progressive non-Hodgkin's lymphoma of indolent type (NHL), previously treated with chemotherapy, received a median of 6 (range 1–9) intravenous infusions of 25 μg/m^2 bryostatin 1 given once weekly over 24 hours. In 14 evaluable patients no responses were seen. Stable disease was attained in one patient for 9 months. The principal toxicities were myalgia and phlebitis. Treatment was discontinued early because of toxicity alone (phlebitis) in 2 patients, toxicity in addition to progressive disease in 3 patients (myalgia and phlebitis $n = 2$; thrombocytopenia $n = 1$) and progressive disease in 5 patients. The results fail to demonstrate efficacy of this regimen of bryostatin 1 in the treatment of NHL. In light of preclinical data that demonstrate synergy between bryostatin 1 and several cytotoxic agents and cytokines, clinical studies to investigate bryostatin 1 in combination are warranted. We also present data to demonstrate that central venous lines may be used in future studies to avoid phlebitis. © 2001 Cancer Research Campaign http://www.bjcancer.com

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Bryostatin 1 is a naturally occurring macrocyclic lactone derived from the marine invertebrate *Bugula neritina* (Pettit et al, 1982). It is a partial agonist of protein kinase C (PKC), a multigene family of isoenzymes with serine-threonine kinase activity that are crucial in cellular signalling pathways and influence proliferation and differentiation (Nishizuka, 1986). Bryostatin 1 induces differentiation of non-Hodgkin's lymphoma cell lines (Mohammed et al, 1993) and has antitumour activity against a variety of human and murine cell lines in vitro in addition to murine models of L10A B cell lymphoma in vivo (Pettit et al, 1982; Hornung et al, 1992). The exact mechanism of action of bryostatin 1 is unclear. It is known that an initial cellular effect is activation and translocation of PKC followed by its down regulation (Berkow et al, 1993). The antitumour effects of bryostatin 1 in vivo may in part be due to immunomodulatory function. For example, the expansion of myeloid and erythroid progenitor cells stimulated by the cytokines GM-CSF, M-CSF and IL-3 is amplified in the presence of bryostatin 1 (May et al, 1987; Sharkis et al, 1990). Similarly, peripheral blood mononuclear cells derived from cancer patients following intravenous infusion of bryostatin 1 have been shown to exhibit enhanced lymphokine activated killer cell activity and proliferation when stimulated by interleukin-2 (Scheid et al, 1994; Jayson et al, 1995). However bryostatin 1 also inhibits production of members of the matrix metalloproteinase family thought to be essential for angiogenesis and metastasis (Wojtowicz-Praga et al, 1997), down-regulates MDR1 gene expression (Al-Katib et al, 1998), modulates bcl-2 and p53 gene expression (Maki et al, 1995) and induces apoptosis (Mohammed et al, 1995) in models of human diffuse large cell lymphoma.

During phase I clinical evaluation of bryostatin 1 antitumour activity was observed in metastatic melanoma (Philip et al, 1993), ovarian cancer and low grade non-Hodgkin's lymphoma (Jayson et al, 1995). The dose-limiting toxicity (DLT) was myalgia and despite several investigations into the aetiology no effective antidote or treatment has been determined for this to date (Hickman et al, 1995; Thompson et al, 1996). Phlebitis was also a significant toxicity and initially attributed to the 60% ethanol formulation used for administration (Prendiville et al, 1993). The subsequent use of a PET formulation (10 μg bryostatin ml^{-1} of 60% polyethylene glycol, 30% ethanol, 10% Tween 80) reduced the incidence of phlebitis (Philip et al, 1993). From these studies a maximum tolerated dose (MTD) of 25 μg/m^2 bryostatin 1 administered by infusion over one hour, weekly, for 3 weeks out of 4 (Philip et al, 1993), or over 24 hours once weekly (Jayson et al, 1995) was established. On the basis of the aforementioned preclinical and phase I data we undertook a phase II study to determine the efficacy of bryostatin 1 in patients with progressive NHL of indolent type.

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Correspondence to: G Jayson

MATERIALS AND METHODS

Patients

Patients eligible for inclusion were aged 18 or over with histologically proven NHL of indolent type, bi-dimensionally measurable

and progressive disease. Patients could have received a maximum of two prior multi-drug chemotherapy regimens. Biopsy at relapse was recommended since the histological grade of NHL can change over time. Histological subtye was classified according to the updated Kiel Classification (Stansfeld et al, 1988). Patients were required to have a WHO performance status of 0–2, a life expectancy of greater than 3 months, a neutrophil count equal to or greater than 1.5×10^9 l^{-1}, platelets equal to or greater than 100×10^9 l^{-1}, serum transaminases less than $2.5 \times$ upper limit of normal, serum bilirubin less than or equal to 20 μM, serum creatinine less than or equal to 120 μM and no toxic manifestations of previous treatment except alopecia. Patients were excluded if they had severe or uncontrolled non-malignant systemic disease, active infection, previous or existing CNS disease, previous or concurrent malignancies except in situ carcinoma of the cervix or adequately treated basal or squamous cell carcinoma of the skin, if pregnant or lactating and if unable to give written informed consent. Concomitant treatment with systemic steroids was not permitted. The study was approved by the Phase I/II Committee and Central Institutional Review Board of the Cancer Research Campaign, the National Cancer Institute, Local Regional Ethics Committees and conducted according to the Declaration of Helsinki. Written informed consent was obtained in all patients. The use of bryostatin had UK Medicines Control Agency approval.

Drug dose and administration

Bryostatin 1 (US National Cancer Institute, Arizona State University/ Cancer Research Institute, USA) was stored at 4°C in vials containing 0.1 mg of lyophilized powder. For administration the lyophilized powder was dissolved in 1 ml of polyethylene glycol 400, ethanol and Tween 80 (PET, 60/30/10 v/v) then further diluted with 0.9% sodium chloride to give a solution containing 10 μg ml^{-1} of bryostatin. This primary solution was further diluted by coinfusion with 1–2 litres of 0.9% saline over 24 hours through a peripheral venous catheter with the infusion rate of bryostatin controlled by a syringe pump. 10 ml polypropylene plastic syringes (SIMS Deltec Inc St Paul, MN, USA) and polyfin extension sets (model 126, Minimed Technologies, CA, USA) were used.

Assessment of toxicity

Investigations performed before commencing therapy included a bone marrow trephine biopsy, full blood count with a differential white cell count, serum biochemistry, urinalysis and chest radiograph. Patients were reviewed by a physician weekly to record new signs and symptoms and document performance status (WHO). A full blood count with differential white cell count and serum biochemistry were repeated weekly. Additional investigations were performed as appropriate. National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) expanded common toxicity criteria were used to grade adverse events except for myalgia, which was graded according to the scale described by Philip et al (1993).

Assessment of tumour response

Evaluable and measurable disease sites were assessed before treatment by physical examination, plain radiography and computerized tomography. Physical examination was repeated weekly and imaging investigations to determine tumour measurements were repeated monthly or at the time of suspected disease progression. Standard WHO criteria for assessment of objective responses were employed (Miller et al, 1981). Patients with progressive disease were withdrawn from the study. Patients were considered evaluable for response if they received 3 or more infusions of bryostatin.

Statistics

To ensure a low probability ($P < 0.05$) of erroneously rejecting a treatment that is active in 20% of patients, a minimum of 14 evaluable patients were treated according to previously described principles (Gehan, 1961).

Bryostatin adsorption studies

The extent of adsorption of bryostatin 1 onto the plastics used was examined. The materials examined were 10 ml polypropylene syringe (SIMS Deltec Inc, St Paul, MN, USA), polyfin extensions sets (MiniMed Technologies, Sylmar, CA, USA) and central venous catheter (Broviac 6.6 Fr single lumen, Bard Ltd, Crawley, UK). Bryostatin 1 solutions were prepared exactly as for clinical drug administration at 10/μg ml and a typical 40 μg dose of bryostatin 1 was used to fill the infusion devices. Following storage at room temperature in standard lighting samples were withdrawn and analysed by UV-HPLC at time points up to 7 days after filling according to previously published methodology (Khan et al, 1998). Concentrations of bryostatin 1 were determined by use of standard curves run immediately before the samples. All plastics were tested in duplicate and duplicate drawn samples from each set were analysed.

RESULTS

Patients

17 patients (10 men, 7 women: age range 39–77 years, median 56, mean 58) with NHL were recruited. 16 patients had previously received chemotherapy including an alkylating agent (≤ 2 single drug regimens; $n = 6$: ≤2 multidrug regimens ± ≥1 single drug regimen; $n = 9$: >2 multidrug regimens; $n = 1$). 7 patients had also received prior radiotherapy, 3 patients had also received biological therapy (vitamin D and/or interferon) and 1 patient had received PUVA therapy. Re-biopsy evidence of low-grade NHL was obtained in 14 patients and all had documented disease progression within 2 months prior to entry to the study. Their characteristics are summarized in Table 1.

Response to treatment

Of 17 patients treated, 14 were evaluable for response. Of those who were not evaluable, 2 patients received less than 3 infusions and 1 patient had received more than 2 previous multidrug regimens. The median number of bryostatin 1 infusions given per patient was 6 (range 1–9) and 7 patients received 8 or more infusions. The outcomes of treatment are summarized in Table 2. No responses (complete or partial) were seen although there were mixed responses in 6 patients with some lesions undergoing shrinkage and others progressing. In one patient disease stabilization was for 9 months. This patient declined further treatment after 8 infusions in order to return to work.

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Table 1 Patient characteristics (n = 17)

Parameter	No. of patients
Sex	
F	7
M	10
Age	median = 56 years (range 39–77)
WHO performance status	
0	11
1	5
2	1
3	0
4	0
Disease sites	
Nodal	13
Nodal and skin	1
Nodal and pleural	1
Nodal and liver	1
Skin	1
Bone marrow involvement	13
Histology	
Follicular	7
Small lymphocytic	4
Other indolent B cell types	6
Previous chemotherapy	
Alkylating agent	16
Anthracycline	4

Toxicity

All patients were included in the analysis of toxicity (Table 3). The main toxicities were myalgia (n = 8) and phlebitis (n = 13). A one week treatment delay and dose reduction (25%) of bryostatin 1 in one patient who had grade 3 myalgia prevented subsequent episodes. The median number of bryostatin infusions given prior to onset of myalgia and phlebitis was 2 (range 1–9) and 1 (range 1–4), respectively. Treatment was withdrawn in 4 patients due to phlebitis. In one patient bryostatin 1 was discontinued after 5 infusions due to grade 2 thrombocytopenia which was possibly treatment related.

Bryostatin adsorption studies

Bryostatin 1 was assayed by our previously published method (Khan et al, 1998). No visible colour changes or precipitate formed upon storage for up to 7 days. There were no additional or apparent decomposition peaks as assessed by HPLC profiles. Adsorption to the polypropylene infusion device, extension set and central venous catheter was very low at 24 hours and upon storage for 7 days there was greater but limited adsorption to the infusion device (Figure 1). This adsorption data is similar to that reported by others (Cheung et al, 1998). It should be noted that PVC shows significant adsorptive properties (Cheung et al, 1998) and our own preliminary work suggests that ethyl vinyl acetate also adsorbs bryostatin 1 (AT McGown, M Ranson, unpublished observations).

DISCUSSION

In this phase II study 17 patients with progressive NHL, previously treated with chemotherapy, received a median of 6 (range 1–9) intravenous 24 hour infusions of 25 μg/m^2 bryostatin 1, given once weekly. 7 patients completed 8 or more infusions. No responses were observed although stable disease was attained in one patient for 9 months. The majority (11/17) of patients were withdrawn from the study because of disease progression and in 5 patients this occurred before 8 infusions of bryostatin 1 had been administered.

The reason for lack of efficacy despite promising preclinical and phase I data, is unclear. Phase II studies of bryostatin 1 given at the same dose but with a one hour infusion in patients with malignant melanoma have also failed to demonstrate significant antitumour activity (Propper et al, 1998; Gonzalez et al, 1999). In contrast, in a phase I trial Varterasian et al (1998) achieved a higher MTD, again limited by myalgia, of 120 μg/m^2 bryostatin 1, infused over 72 hours every 2 weeks. A phase II trial of this regimen was recently reported documenting one complete remission of 18 months and two partial remissions of greater than 6 months duration in patients with low grade NHL (Varterasian et al, 2000). Lack of efficacy of bryostatin 1 in the current study may therefore be due to suboptimal dose and duration of treatment but antitumour

Table 2 Outcome of treatment with bryostatin (n=17)

Patient	Number of infusions (weeks on treatment)	Reason off study	Response
1	5 (6**)	PD	PD
2	6 (6)	Toxicity (phlebitis + myalgia) + PD	PD*
3	4 (4)	Toxicity (phlebitis + myalgia) + PD	PD
4	6 (7**)	PD	PD
5	8 (8)	PD	PD
6	5 (5)	Toxicity (thrombocytopenia) + PD	PD*
7	2 (2)	PD	Not evaluable
8	8 (8)	PD	PD
9	9 (10**)	PD	PD
10	3 (3)	PD	PD
11	8 (8)	PD	PD
12	1 (1)	Toxicity (phlebitis)	Not evaluable
13	5 (5)	Toxicity (phlebitis)	Not evaluable
14	9 (11**)	PD	PD
15	8 (8)	Declined further treatment	Stable disease
16	8 (9**)	PD	PD
17	3 (4**)	PD	PD

*Clinical evidence of disease progression, objective measurements were not evaluable. **Patients in whom treatment delays occurred. PD = progressive disease.

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Table 3 Toxicities associated with bryostatin treatment ($n = 17$)

	Number of patients				
NCIC – CTG Grade*	**0**	**1**	**2**	**3**	**4**
Myalgia**	9	4	3	1	0
Phlebitis	4	1	10	2	0
Headache	14	3	0	0	0
Fatigue	12	5	0	0	0
Nausea/vomiting	13	4	0	0	0
Diarrhoea	16	1	0	0	0
Thrombocytopenia	15	1	1	0	0
Leucopenia	15	2	0	0	0
Bilirubin	16	0	0	1	0
Neuralgia	16	1	0	0	0

*National Cancer Institute of Canada Clinical Trials Group expanded toxicity scale. **Graded according to Philip et al (1993).

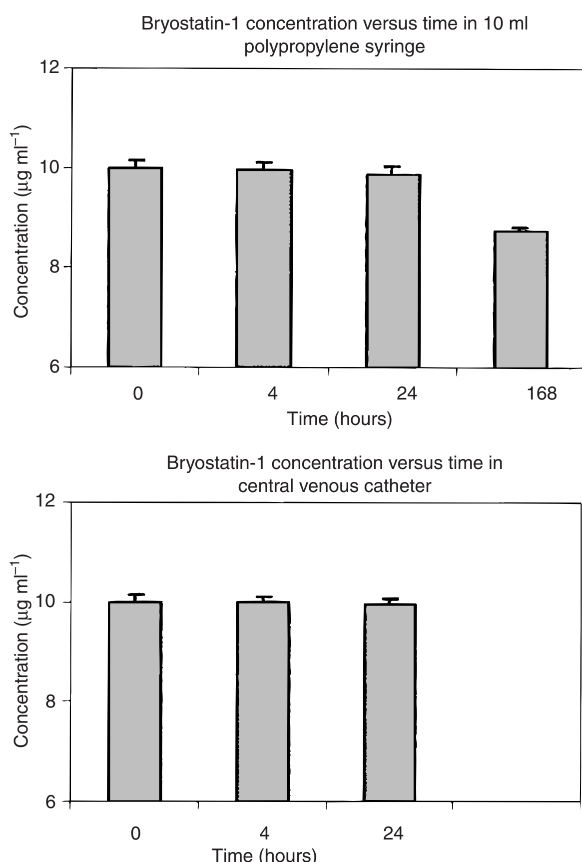

Figure 1 Adsorption of bryostatin 1 onto infusion devices

activity was observed during phase I evaluation using both 1 and 24 hour infusions of 25 μg/m^2 bryostatin 1 (Philips et al, 1993; Jayson et al, 1995). As there is no established method to reliably determine serum concentrations of bryostatin 1 in humans it has not been possible to obtain pharmacokinetic data to determine serum concentrations and rationally optimize the schedule. Animal data suggest that bryostatin 1 has a short plasma half life (Berkow et al, 1993) with in vitro and in vivo data showing enhanced antitumour effects on prolonged exposure (Hornung et al, 1992) and the data of Varterasian et al would support this. However, it is perplexing that significant differences in MTD of bryostatin 1 have been demonstrated despite consensus regarding toxicity. In addition to the aforementioned studies a MTD of 44 μg/m^2 bryostatin 1 administered over 1 hour weekly for 3 weeks out of 4 has been reported in a paediatric oncology group study (Weitman et al, 1999). The significant adsorption of bryostatin 1 onto polyvinyl chloride and ethyl vinyl acetate (Cheung et al, 1998) raises the possibility that differences in adsorptive properties of administration devices used may account for discrepancies in MTD observed. Compared with other studies, phlebitis was a significant toxicity in this study. We chose a peripheral vein for drug administration due to uncertainty over the adsorption of bryostatin onto material used for central infusion devices but have subsequently demonstrated that the adsorption of bryostatin onto small (10 ml) polypropylene infusion devices and a central infusion catheter is negligible over 24 hours (Figure 1). Central administration may therefore be safely used to avoid phlebitis; however materials used for infusion of bryostatin 1 should be clearly stated in all reports of clinical trials.

Further explanations for lack of efficacy of bryostatin 1 in this study include suppressed lymphocyte function due to lymphoma or previous chemotherapy and radiotherapy which may have prevented bryostatin 1 from acting through immune stimulatory mechanisms (Propper et al, 1998). In addition the modulation of tumour-specific PKC isoenzyme profiles by bryostatin 1 is poorly understood. PKC isoenzymes are involved in both oncogene and tumour suppressor gene activation, variable expression of PKC isotypes in tumours has been demonstrated and the degree to which isotypes are downregulated by bryostatin 1 also varies (Buchner, 2000). Bryostatin 1 may only be effective when targeted to individuals bearing tumours with particular PKC isoenzyme profiles.

The efficacy of bryostatin 1 may be enhanced by administration in combination. For example, pretreatment with bryostatin 1 increases the cytotoxicity of 2-chlorodeoxyadenosine in drug-resistant chronic lymphocytic leukaemia cells (Mohammed et al, 1998), cisplatin in human cervical carcinoma cells (Basu and Lazo, 1992) and cytarabine in fresh blast cells from patients with acute myeloid leukaemia (Elgie et al, 1998). In a tumour-bearing mouse model enhanced cytotoxicity is observed when bryostatin 1 is administered following paclitaxel (Koutcher et al, 2000); synergy between bryostatin 1 and tamoxifen, which also inhibits PKC, has been demonstrated in the drug resistant P388 leukaemia cell line which lacks steroid receptors (McGown et al, 1998) and vincristine in combination with bryostatin 1 has been shown to cure mice bearing xenografts of neoplastic B cells derived from human Waldenströms macroglobulinaemia (Mohammed et al, 1994). On this basis, Varterasian et al (2000) conducted a feasibility study in which patients who developed progressive NHL while receiving single agent bryostatin were given sequential treatment with vincristine. Doses of up to 2 mg/m^2 vincristine were well tolerated with no unexpected or enhanced toxicity. Similarly, in early reports of phase I trials, bryostatin 1 in combination with paclitaxel or cisplatin appears to be well tolerated and myalgia has occured less frequently than in single agent trials (Kaubisch et al, 1999; Rosenthal et al, 1999).

In summary, this study failed to show a significant benefit from single agent bryostatin 1 in progressive NHL of indolent type. Improved understanding of bryostatin 1 pharmacokinetics and

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modulation of tumour PKC isotypes by bryostatin 1 would probably aid development of this novel agent. Further evaluation of bryostatin 1 in combination is warranted.

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