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Brostallicin, an agent with potential activity in metastatic soft tissue sarcoma: A phase II study from the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group

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ABSTRACT

The study aimed to assess the efficacy and safety of brostallicin, a new DNA minor groove binder, at a dose of 10 mg/m^2, intravenous (i.v.) every three weeks, in patients with advanced or inoperable soft tissue sarcoma (STS) and gastrointestinal stromal tumour (GIST) failing first line therapy. Two groups were recruited: (1) GIST following treatment with imatinib; (2) other STS following treatment with single agent doxorubicin or ifosfamide or a single line of combination therapy. The primary end-point was overall response rate (ORR) as defined by response evaluation criteria in solid tumours (RECIST). Progression free survival (PFS) was a secondary end-point. In the GIST group, a Simon two step design was planned: first step 18 patients, total 32 patients ($p1 = 20\%$ $p0 = 5\%$ alpha = beta = 0.1). In the non-GIST group, planned sample size was 40 in a standard Fleming one-step design ($p0 = 10\%$, $p1 = 25\%$, alpha = beta = 0.1). Forty-three patients with non-GIST and 21 patients with GIST were recruited. In general, the drug was well tolerated. Common Toxicity Criteria (CTC) grade 3 or grade 4 toxicity was granulocytopenia: 70% of patients, 50% of cycles; fatigue: 25% of patients, 8% of cycles; febrile neutropenia: 14% of patients, 4% of cycles. There was one confirmed toxic death due to neutropenic septicaemia. Three patients had clinically significant allergic reactions in 249 cycles delivered. In the GIST group, no patients had a confirmed response and recruitment was discontinued at the first step. In the non-GIST group, there were two confirmed partial responses. The 3 month PFS was 46% in the non-GIST group and 33% in the GIST group. In the non-GIST

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group, this PFS is in the range of other agents considered active in STS, and may predict for more substantial first line activity. Further investigation in STS other than GIST appears warranted.

1. Introduction

The portfolio of drugs with established activity in soft tissue sarcoma remains regrettably small. Clinical studies of doxorubicin, ifosfamide and dacarbazine given individually in first line therapy for metastatic or locally advanced inoperable sarcoma report ORR of 15–25%.[1] In second line, the reported ORR to these and other agents do not exceed 10% in multi-centre studies.[2] Combination therapy may increase the response rate but has not been shown to improve survival.[3] With the remarkable exception of imatinib for patients with gastrointestinal stromal tumour,[4] there has been little progress in the development of systemic therapy for sarcoma over the last 30 years, only trabectidin (ET-743, Yondelis) has been suggested to yield tumour control rates of the magnitude achieved with the other active agents. Some patients clearly gain worthwhile benefit from chemotherapy but reliable predictive criteria have not yet been discovered.

Brostallicin is a novel compound initially developed by Pharmacia and Upjohn and now by Nerviano Medical Sciences. It is a member of a relatively new class of cytotoxic drugs which bind to the minor groove of DNA causing lesions that trigger apoptosis. It is a synthetic a-bromoacrylic derivative of a distamycin-like structure having four pyrrolocarbamoyl units ending with a guanidino moiety.[5]

Pre-clinical work suggests that this compound may have relatively superior activity in tumours characterised by drug resistance, in particular, drug resistance mediated through glutathione and glutathione related enzymes.[6] Brostallicin interacts with glutathione in a critical way that may enhance its cytotoxicity and *in vitro* experiments demonstrated superior cytotoxicity in drug resistant cell lines compared to other standard cytotoxics. The maximum tolerated dose (MTD) from the phase 1 study was 10 mg/m^2 in a 21 day cycle.[7] The activity of brostallicin has been investigated in head and neck cancer and lung cancer, but further work in sarcoma was undertaken because of the high level of glutathione and glutathione related enzymes in soft tissue sarcomas and because of a single patient with a GIST who achieved a confirmed partial tumour response during phase I testing of the drug.[7]

In the present study by the Soft Tissue and Bone Sarcoma Group (STBSG) of the European Organisation for the Research and Treatment of Cancer (EORTC), the clinical activity of brostallicin was tested in patients with soft tissue sarcoma. The objective of the study was to screen for anti-tumour activity of brostallicin in patients with locally advanced or metastatic soft tissue sarcoma who had failed one prior chemotherapy treatment. The primary end-point was overall response rate. Time to tumour progression, duration of objective response and the safety profile of brostallicin were pre-defined secondary endpoints.

2. Patients and methods

2.1. Eligibility criteria

Two parallel cohorts were recruited: (1) patients with histologically confirmed GIST and (2) patients with other histotypes of soft tissue sarcoma including malignant fibrous histiocytoma (now called undifferentiated pleomorphic sarcoma), liposarcoma, rhabdomyosarcoma, synovial sarcoma, malignant paraganglioma, fibrosarcoma, leiomyosarcoma, angiosarcoma, haemangiopericytoma, malignant peripheral nerve sheath tumour, unclassified sarcoma and miscellaneous sarcoma, but excluding GIST, mixed mesodermal tumours of the uterus (and carcinosarcoma), chondrosarcoma, malignant mesothelioma, neuroblastoma, osteosarcoma, Ewing's sarcoma and embryonal rhabdomyosarcoma.

The principle inclusion criteria were as follows. All patients had locally advanced and/or metastatic disease with confirmed progression: in the GIST group, while on treatment with imatinib mesylate; and in the non-GIST group after treatment with either single agent doxorubicin or ifosfamide or with a single line of a combination regimen containing doxorubicin and ifosfamide. A minimum interval of four weeks was required between last treatment with imatinib or chemotherapy (as appropriate) and study entry. The other eligibility criteria were the same for both groups and included disease not amenable to treatment of curative intent, at least one measurable lesion according to RECIST criteria,[8] no ongoing acute toxicity from previous chemotherapy (except alopecia), age >15 years, WHO performance status <2, white blood cells (WBC) $\geqslant 4 \times 10^9$/l, platelets $>100 \times 10^9$/l, serum creatinine $\leqslant 120$ μmol/l, or calculated glomerular filtration rate >65 ml/min, serum bilirubin $\leqslant 1.25\times$ upper limit of normal (ULN), serum glutamate oxaloacetate transaminase (SGOT) and serum glutamate pyruvatw transaminase (SGPT) $\leqslant 3.0 \times$ ULN, serum alkaline phosphatase $\leqslant 2.5\times$ ULN. Research ethics approval was obtained from central and local committees and all patients gave written, informed, consent.

2.2. Pre-study and on-study investigations

Prior to study start, all patients had 12 lead electrocardiogram (ECG), chest X-ray, complete medical history and physical examination, routine biochemistry and haematology profiles, pregnancy test (if indicated) and contraceptive counselling. Local histological diagnosis was accepted for trial entry but central histological review was performed where possible, according to EORTC STBSG standard procedure. All patients had tumour assessment by computerised axial tomography (CT) scan or other appropriate modality with in 28 days of starting treatment. Routine biochemical and

haematological monitoring was performed within 14 days of starting treatment, on day one of each cycle and weekly during treatment. Patients had medical review and physical examination on day one of each cycle of treatment. Toxicity was graded according to National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2. Tumour assessments were repeated with the same modality as at baseline at least after every two cycles of treatment and response was graded according to RECIST criteria.[8] All responses would be reviewed by an independent peer.

2.3. Treatment details

Brostallicin was administered as a slow intravenous infusion over 10 min at a starting dose of 10 mg/m^2 on a 21 day cycle. Dose delay and reduction criteria were as follows: retreatment was to be delayed if absolute neutrophil count (ANC) $<1.5\times10^9$/l or platelets $<100\times10^9$/l at day 21 or if there was any non-haematological toxicity >grade 1. Treatment could be delayed up to two weeks. If toxicity had not resolved by then the patient was not retreated. Dose was to be reduced to 7.5 mg/m^2 if there was grade 4 neutropenia which had not recovered by day 28, grade 3 or grade 4 thrombocytopenia, or any episode of febrile neutropenia. Dose reduction was also mandated for any grade 2 neurotoxicity, or any other grade 3 or grade 4 non-haematological toxicity. There was provision for dose escalation to 12.5 mg/m^2 at cycle 2 if all toxicity was $\leqslant$grade 1 on a case by case basis in discussion with the study co-ordinator. Prophylactic anti-emetic treatment with a $5HT_3$ antagonist was recommended. Prophylactic treatment with haematopoietic growth factors was not permitted. Patients were allowed to continue on treatment until there was progressive disease, unacceptable toxicity or the patient withdrew voluntarily.

2.4. Statistical design

For the cohort with GIST, a two-stage Simon design was applied.[9] A total of 18 eligible patients starting with protocol therapy were required for the first step. The study would be temporarily closed at this point and only reopened if at least one response was observed; a total of 32 eligible patients starting with therapy would then be required. This design has the power to detect a response rate of 20% or greater and exclude a response rate of 5% or less with alpha = beta = 0.1.

For the cohort with soft tissue sarcoma other than GIST, a standard one-stage Fleming design was adopted.[10] This group was powered to detect an ORR of 25% ($p1$) and exclude an ORR of 10% ($p0$) or less with alpha = beta = 0.1. To do this it was planned to recruit 40 patients, evaluable for response. If more than six of these patients had a confirmed response, then the stated efficacy threshold would have been attained.

Time to progression was defined as from the date of treatment start to the first date of documented progression by RECIST criteria.[8] Progression free survival was calculated using the Kaplan–Meier method.[11]

The trial was run to ICH GCP standards with an unrestricted educational grant from Pharmacia.

3. Results

3.1. Patients

Recruitment was complete in six months in the non-GIST group and reached the end of the first stage in 11 months in the GIST group. In total an entry of 64 patients was made (21 GIST, 43 non-GIST). Patient characteristics are shown in Table 1.

Table 1 – Patient characteristics

	GIST	Other STS
Number of patients	21	43
Median age	48 years (range 27–70)	51 years (range 25–75)
Sex	14 M:7 F	19 M:24 F
PS 0/1	8/13	23/20
Prior adjuvant chemotherapy	2	3
Prior radiotherapy including haematopoietic sites	0	3
Prior radiotherapy excluding haematopoietic sites	2	13
Referral histology	GIST: 21	Undifferentiated sarcoma and Sarcoma (NOS): 11 Synovial sarcoma: 9 Leiomyosarcoma: 9 Liposarcoma: 6 MFH: 2 Rhabdomyosarcoma: 1 Fibrosarcoma: 1 Angiosarcoma: 1 Other histotypes: 3
Review histology confirmation	Agreement:14/15 Major disagreement 1/15	Agreement: 26/38 Minor disagreement: 10/38 Major disagreement: 2/38

STS, soft tissue sarcoma; M, male; F, female; PS, performance status; MFH, malignant fibrous histiocytoma (now called undifferentiated pleomorphic sarcoma); NOS, not otherwise specified.

Histological review was performed on 53 cases. There was a minor disagreement (change of histotype of sarcoma) in 10 cases and a major disagreement in three (GIST to PEComa; undifferentiated sarcoma to melanoma; unclassified sarcoma to osteosarcoma). These last three cases were regarded as ineligible for the purposes of response assessment but have been included in the toxicity assessment. There were therefore 63 patients eligible and evaluable for assessment of toxicity (one patient excluded as received no treatment). There were 18 patients with GIST who were eligible and evaluable for response (three exclusions: one due to non-eligible histology, two due to protocol violations). There were 40 patients in the non-GIST group eligible and evaluable for response (three exclusions: two non-eligible histologies, one never received treatment).

3.2. *Treatment*

A total of 249 cycles of treatment were given. In the GIST group, 21 patients received treatment. Twelve patients discontinued treatment after one or two cycles, six patients had six or more cycles of which two had 10 or more. In the non-GIST group, one patient never started treatment, 18 out of 43 discontinued treatment after one or two cycles, 10 had six or more cycles, of which three had 10 or more (Table 2).

Table 2 – Treatment details

	GIST	Non-GIST
Never started		1
Discontinued after 1 or 2 cycles	12	18
Received 3–5 cycles	3	14
Received 6 or more	6	10
Received 10 or more	2	3

3.3. *Toxicity*

For the purposes of toxicity, the two groups of patients have been combined.

Thirty of 63 patients had their treatment on time and at full dose (48%). Twenty-four patients (38%) had at least one dose delay without dose reduction and 9 (14%) patients had dose reduction or both delay and dose reduction. In the majority of patients this was due to reversible haematological toxicity.

Following the first dose, 42 patients (67%) had grade 3 or grade 4 granulocytopenia and 10 had grade 3 or grade 4 thrombocytopenia (16%) (Tables 3 and 4). Nine patients had at least one episode of febrile neutropenia (14%). In a total of 245 reported cycles (4 missing), 122 cycles were complicated by grade 3 or grade 4 granulocytopenia (50%) and 20 cycles by grade 3 or grade 4 thrombocytopenia (8%). A total of 10 febrile neutropenic events were reported in the whole study (4% of cycles). There was one toxic death due to sudden catastrophic septic shock. Fatigue was the commonest non-haematological toxicity (grade 3 or grade 4: 16 patients, 25%; 19 of 247 cycles, 8%). Six patients had hyperbilirubinaemia grade 3 or grade 4 (10%) in 6 of 243 cycles (2%) (Table 5).

Three patients (4.8%) had CTC grade 4 acute allergic reactions during infusion of the drug characterised by sweating, flushing and hypotension and breathlessness during cycles 3, 6, and 9. As these appeared to be related to later cycles of treatment and occurred in two of the 11 patients who had received more than six cycles of therapy (18.2%), investigators were advised to pre-medicate patients with intravenous steroid and anti-histamine if continuing therapy beyond five cycles. Although the numbers are small, this intervention appeared to reduce the incidence of further allergic reactions. Rechallenge with brostallicin after an allergic reaction was performed in two patients without further problems. No patient had more than transient symptoms

Table 3 – Haematological events per patient – first cycle of therapy

	0	1	2	3	4	Total
Leucopenia	7 (11%)	12 (19%)	16 (25%)	18 (29%)	10 (16%)	63
Granulocytopenia	8 (13%)	5 (8%)	8 (13%)	13 (21%)	29 (46%)	63
Thrombocytopenia	37 (59%)	6 (10%)	10 (16%)	6 (10%)	4 (6%)	63
Anaemia	5 (8%)	39 (62%)	17 (27%)	2 (3%)	–	63

Table 4 – All haematological events (each row first line = patients, second line = cycles)

CTC grade	Missing	0	1	2	3	4	Total
Leucopenia	0	4 (6%)	14 (22%)	15 (24%)	19 (30%)	11 (18%)	63
	4 (1%)	51 (20%)	56 (22%)	82 (33%)	43 (17%)	13 (5%)	249
Granulocytopenia	0	5 (8%)	7 (11%)	7 (11%)	14 (22%)	30 (48%)	63
	4 (2%)	45 (18%)	28 (11%)	50 (20%)	73 (29%)	49 (20%)	249
Thrombocytopenia	0	34 (54%)	6 (9.5%)	11 (17.5%)	7 (11.1%)	5 (7.9%)	63
	4 (2%)	169 (68%)	28 (11%)	28 (11%)	12 (5%)	8 (3%)	249
Anaemia	0	3 (4.8%)	25 (39.7%)	27 (42.9%)	7 (11.1%)	1 (1.6%)	63
	4 (2%)	31 (12%)	133 (53%)	72 (29%)	8 (3%)	1 (1%)	249

Table 5 – Clinical events >10% of patients (first line = worst grade per patient, second line = cycles)

CTC grade	Missing	0	1	2	3	4	Total
Allergy	0	58 (92.1%)	1 (1.6%)	1 (1.6%)	–	3 (4.8%)	63
	2 (0.8%)	243 (97.6%)	–	1 (0.4%)		3 (1.2%)	249
Odema	0	51 (81%)	10 (15.9%)	0	2 (3.2%)	–	63
	2 (0.8%)	228 (91.6%)	16 (6.43%)	1 (0.4%)	2 (0.8%)		249
Lethargy	0	5 (7.9%)	18 (28.6%)	24 (38.1%)	15 (23.8%)	1 (1.6%)	63
	2 (0.8%)	89 (35.7%)	74 (29.7%)	65 (26.1%)	17 (6.8%)	2 (0.8%)	249
Fever	0	47 (74.6%)	10 (15.9%)	6 (9.5%)	–	–	63
	2 (0.8%)	228 (91.6%)	12 (4.8%)	7 (2.8%)			249
Sweating	0	52 (82.5%)	6 (9.5%)	5 (7.9%)	–	–	63
	2 (0.8%)	229 (92%)	12 (4.8%)	6 (2.4%)			249
Alopecia	0	47 (74.6%)	8 (12.7%)	8 (12.7%)	–	–	63
	2 (0.8%)	214 (85.9%)	19 (7.6%)	14 (5.6%)			249
Rash	0	53 (84.1%)	4 (6.3%)	6 (9.5%)	–	–	63
	2 (0.8%)	237 (95.1%)	4 (1.6%)	6 (2.4%)			249
Other dermatologic	0	49 (77.8%)	9 (14.3%)	3 (4.8%)	2 (3.2%)	–	63
	2 (0.8%)	222 (89.1%)	20 (8.0%)	3 (1.2%)	2 (0.8%)		249
Anorexia	0	39 (61.9%)	14 (22.2%)	8 (12.7%)	2 (3.2%)	–	63
	2 (0.8%)	194 (77.9%)	34 (13.6%)	17 (6.8%)	2 (0.8%)		249
Constipation	0	33 (52.4%)	16 (25.4%)	13 (20.6%)	1 (1.6%)	–	63
	2 (0.8%)	199 (79.9%)	21 (8.4%)	26 (10.4%)	1 (0.4%)		249
Diarrhoea	0	49 (77.8%)	11 (17.5%)	2 (3.2%)	1 (1.6%)	–	63
	2 (0.8%)						249
Nausea	0	24 (38.1%)	23 (36.5%)	15 (23.8%)	1 (1.6%)	–	63
	2 (0.8%)	172 (69.1%)	56 (22.5%)	18 (7.2%)	1 (0.4%)		249
Stomatitis	0	45 (71.4%)	9 (14.3%)	8 (12.7%)	1 (1.6%)	–	63
	2 (0.8%)	220 (88.3%)	16 (6.4%)	10 (4.0%)	1 (0.4%)		249
Vomiting	0	35 (55.6%)	14 (22.2%)	8 (12.7%)	6 (9.5%)	–	63
	2 (0.8%)	203 (81.5%)	28 (11.2%)	10 (4.0%)	6 (2.4%)		249
Other GI events	0	47 (74.6%)	8 (12.7%)	5 (7.9%)	3 (4.8%)	–	63
	2 (0.8%)	228 (91.6%)	9 (3.6%)	7 (2.8%)	3 (1.2%)		249
Febrile neutropenia	0	54 (85.7%)	–	0	8 (12.7%)	1 (1.6%)	63
	2 (0.8%)	237 (95.2%)		1 (0.4%)	8 (3.2%)	1 (0.4%)	249
Infection without neutropenia	0	50 (79.4%)	2 (3.2%)	9 (14.3%)	2 (3.2%)	–	63
	2 (0.8%)	232 (93.2%)	3 (1.2%)	10 (4.0%)	2 (0.8%)		249
Other infection	0	54 (85.7%)	3 (4.8%)	3 (4.8%)	3 (4.8%)	–	63
	2 (0.8%)	237 (95.2%)	3 (1.2%)	4 (1.6%)	3 (1.2%)		249
Dizziness	0	53 (84.1%)	8 (12.7%)	1 (1.6%)	1 (1.6%)	–	63
	2 (0.8%)	235 (94.4%)	10 (4.0%)	1 (0.4%)	1 (0.4%)		249
Neuropathy – sensory	0	54 (85.7%)	6 (9.5%)	2 (3.2%)	1 (1.6%)	–	63
	2 (0.8%)	234 (94.0%)	8 (3.2%)	4 (1.6%)	1 (0.4%)		249
Other neurological events	0	48 (76.2%)	6 (9.5%)	7 (11.1%)	2 (3.2%)	–	63
	2 (0.8%)	222 (89.2%)	12 (4.8%)	11 (4.4%)	2 (0.8%)		249
Chest pain	0	54 (85.7%)	7 (11.1%)	–	2 (3.2%)	–	63
	2 (0.8%)	237 (95.2%)	8 (3.2%)		2 (0.8%)		249
Headache	0	47 (74.6%)	8 (12.7%)	6 (9.5%)	2 (3.2%)	–	63
	2 (0.8%)	228 (91.6%)	9 (3.6%)	8 (3.2%)	2 (0.8%)		249
Myalgia	0	55 (87.3%)	3 (4.8%)	4 (6.3%)	1 (1.6%)	–	63
	2 (0.8%)	233 (93.6%)	3 (1.2%)	10 (4.0%)	1 (0.4%)		249
Other pain	0	37 (58.7%)	11 (17.5%)	11 (17.5%)	3 (4.8%)	1 (1.6%)	63
	2 (0.8%)	195 (78.3%)	33 (13.2%)	14 (5.6%)	4 (1.6%)	1 (0.4%)	249
Cough	0	45 (71.4%)	12 (19%)	3 (4.8%)	3 (4.8%)	–	63
	2 (0.8%)	220 (88.3%)	16 (6.4%)	8 (3.2%)	3 (1.2%)		249

Table 5 – continued

CTC grade	Missing	0	1	2	3	4	Total
Dyspnoea	0	39 (61.9%)	–	16 (25.4%)	6 (9.5%)	2 (3.2%)	63
	2 (0.8%)	210 (84.3%)		28 (11.2%)	7 (2.8%)	2 (0.8%)	249
Renal/GU events	0	56 (88.9%)	5 (7.9%)	1 (1.6%)	1 (1.6%)	–	63
	2 (0.8%)	237 (95.2%)	7 (2.8%)	1 (0.4%)	1 (0.4%)		249
Other events	0	48 (76.2%)	7 (11.1%)	5 (7.9%)	3 (4.8%)	0 (0%)	63
	2 (0.8%)	226 (90.8%)	11 (4.4%)	7 (2.8%)	3 (1.2%)	0 (0%)	249

and none were admitted for in-patient care as a result of an allergic reaction.

3.4. *Efficacy*

Efficacy is reported separately for each group excluding ineligible patients and one patient who did not receive any therapy (Table 6).

3.4.1. *GIST group*

There were no objective regressions observed in 18 patients evaluable for response in the first step of the GIST group and recruitment was therefore not reopened for the second step. Eight patients (42%) had stable disease at first assessment and 6 (32%) remained on therapy with stable disease at a minimum of 18 weeks. Two patients had prolonged stabilisation of disease with no evidence of progression until 7.5 months and 12 months (see Fig. 1).

The median time to progression for the whole group was 67 days (range 38–157). The three month progression free estimate was 33% (s.e. 11%) and the 6 month progression free rate was 21% (s.e. 10%). Median survival in the GIST group was 298 days (range 188 – not reached).

3.4.2. *Non-GIST group*

In 40 patients evaluable for response in the non-GIST group, two patients (5%) had a partial response and 20 (50%) had stable disease at their first tumour assessment. The median time to progression for the whole group of assessable patients ($n = 40$) was 88 days (range 42–113). The three month progression free estimate was 46% (standard error (s.e.) 8%) and the six month progression free rate was 22% (s.e. 7%).

Table 6 – Response data

	GIST	Non-GIST
CR	0	0
PR	0	2
SD / NC	8	20
PD	10	17
NE	1	0
Early death	0	1
3 month PFS	33% (s.e. 11%)	46% (s.e. 8%)
6 month PFS	21% (s.e. 10%)	22% (s.e. 7%)

CR, complete response; PR, partial response; SD, stable disease; NC, no change; PD, progressive disease; NE, not evaluable.

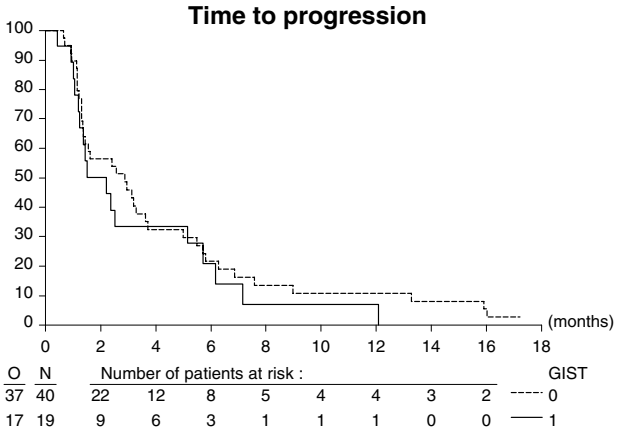

Fig. 1 – Time to tumour progression (eligible treated patients).

Median survival in the non-GIST group was 231 days (range 159–421).

4. Discussion and conclusions

The study demonstrates that brostallicin has an acceptable toxicity profile even in pre-treated patients. Significant (grade 3 or grade 4) myelosuppression was more common than expected from the phase I study and presumably reflects more aggressive pre-treatment in the group of patients studied. However, febrile neutropenia was infrequent. The toxic death appears to have been due to an extremely virulent staphylococcal infection and was, we believe, an exceptional event. The appearance of allergic drug reactions in patients receiving more prolonged treatment was not predicted by previous studies but was controllable with appropriate pre-medication.

In the non-GIST group, two objective responses have been observed amongst 43 patients. This excludes the possibility (beta = 0.1) of a 25% response rate in this group of patients. In the GIST group, despite the response seen in the phase I trial, no responses were observed in the first 19 patients and this excludes the possibility (beta = 0.1) of a 20% response rate in this group of patients. The trial therefore failed to show evidence of efficacy in both groups according to the primary end-point.

The primary end-point chosen in this trial was the classical end-point of objective tumour response. While this is undeniably a valid methodology, it is increasingly recognised that this approach may fail to detect worthwhile activity which

slows tumour progression, with associated improvement in survival, without tumour shrinkage. It is now increasingly recognised that the demonstration of response is a relatively crude screening tool, reliant upon criteria that were developed 30 years ago, before the advent of accurate cross-sectional imaging and prior to the arrival of many anti-cancer agents whose activity is likely to be cytostatic rather than cytocidal.[12] As such, this tool may have high selectivity but poor sensitivity and there is therefore a substantial risk of false negative results with consequent premature termination of a new drug's development. New or modified methodology may be required.

In a retrospective analysis of 11 agents investigated by the EORTC STBSG, van Glabbeke found that patients treated with either of the two agents with known clinical activity in the first-line (doxorubicin and ifosfamide) had significantly prolonged progression free survival at 3 and 6 months compared to patients treated with agents classed as inactive. It was therefore suggested that 3 PFS > 40% and 6 month PFS > 20% in the second line might be a signal for clinically significant benefit in first line therapy.[13]

In this trial, PFS was a pre-selected secondary end-point and, in the non-GIST group, there was progression arrest and prolongation of stable disease in a remarkable number of patients. The progression free rate at three months is above 40% and the six month progression free rate is above 20%. This agent therefore segregates with the active agents identified in the retrospective by van Glabbeke and is significantly different from those agents classed as inactive.[13] It is intriguing that the only other agent to be found to have a similar activity in soft tissue sarcoma using this index is trabectidin[14], another DNA minor groove binder.

Progression free survival (PFS) was not the primary end-point in this study because, at the time of protocol development, this was not yet a commonly accepted end-point for clinical trials. In the mean time, the situation has changed, and PFS is now a standard primary end-point for EORTC-STBSG phase II trials as well as those of other sarcoma groups.

This study tested patients with GIST separately from other histotypes of sarcoma: however, in common with most clinical trials of novel agents in soft tissue sarcoma to date, the non-GIST group was a mixture of histological sub-types. It is now recognised that different histotypes of sarcoma demonstrate different sensitivities to different agents and should therefore perhaps be treated differently.[15,16] This is a potential limitation of the current trial. In the current study, the non-GIST group is too small to subject to further sub-group analysis. It has now become a standard aspect of protocol design within the EORTC STBSG to include different strata for the main sub-types of soft tissue sarcoma.

In conclusion, this study has demonstrated that brostallicin has a manageable toxicity profile and although objective tumour responses were infrequent, the drug may warrant further investigation in view of the measured three month PFR of about 40% in a group of patients with a range of other soft tissue sarcoma histotypes.

Conflict of interest statement

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