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ORIGINAL ARTICLE

Clinical benefit of early phase clinical trial participation for advanced sarcoma patients

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Abstract
Purpose Standard systemic treatment options for patients with advanced sarcoma are limited. Depending on the histological subtype, patients receive differing lines of therapy usually consisting of doxorubicin, ifosfamide and/or trabectedin. After progression on conventional therapies, some patients are offered more experimental options including Phase I clinical trials. The aim of this study was to evaluate the clinical benefit for sarcoma patients treated within the Phase I Unit of a single referral centre.
Methods The response, toxicity and outcome of sarcoma patients treated within Phase I clinical trials at the Royal Marsden between August 1998 and December 2010 were analysed.
Results One hundred and thirty-three patients were treated. The median number of prior systemic therapies was 3 (range 0–6). The median age of these patients was 48.0 years (range 12.5–81.9), with a male/female ratio of 71/62. One patient (0.8%) achieved a complete response and 2 (1.6%) partial responses. The non-progression rate at 3 and 6 months was 31.5% (95% CI, 23.4–39.6%) and 11.0% (95% CI 5.6–16.5%), respectively. The median progression-free survival was 2.1 months (95% CI, 1.7–2.5), and median overall survival was 7.6 months (95% CI, 4.8–10.4). Twenty-four (18.0%) patients experienced grade 3 or 4 toxicity, and 16 (12.0%) stopped trial treatment due to toxicity.
Conclusion Phase I clinical trials could be considered a therapeutic option in sarcoma patients with no remaining standard treatment due to the low risk of toxicity and the potential for clinical benefit.

Keywords Sarcoma · Phase I · Response · Toxicity · Progression-free survival · Overall survival

Purpose

Sarcomas are a group of heterogeneous mesodermal malignancies that encompass a diverse range of different histological subtypes [1]. For early stage sarcoma surgical resection remains the mainstay of treatment. However, in the metastatic setting, systemic treatment with chemotherapy is the main treatment option for many sarcoma subtypes. Doxorubicin and ifosfamide have shown reproducible activity in treating sarcomas [2]. Recently, trabectedin, a natural marine-derived product, has emerged as an active agent, particularly in some subtypes such as myxoid/round cell liposarcoma, refractory to anthracyclines and ifosfamide [3, 4]. In addition, other histological subtypes could be offered other systemic therapy regimens, such as gemcitabine

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and docetaxel in leiomyosarcoma and pegylated liposomal doxorubicin in angiosarcoma [2, 5].

The utility of imatinib [6] and sunitinib [7] in gastro intestinal stromal tumours (GIST) has highlighted the potential for novel targeted agents to revolutionise the treatment of a rare disease previously assigned as resistant to systemic therapy [2]. Other emerging molecularly targeted drugs have shown promising results in early trials, such as IGF1-R (Insulin-like Growth Factor-1 Receptor) monoclonal antibodies in Ewing's sarcoma [8, 9]. However, there still remains a pressing need for new therapeutic approaches in other sarcoma subtypes.

Phase I oncology clinical trails are dose-finding and toxicity-defining studies, primarily designed to establish a safe dose and schedule for further evaluation in Phase II trials, although sometimes Phase I trials can also have pharmacokinetic or pharmacodynamic objectives as primary aims. Furthermore, antitumour activity derived from these trials is never considered the primary endpoint, but both patients and clinicians actively seek clinical activity.

Currently, there is little published data on the clinical benefit and risk derived by sarcoma patients treated within Phase I trials [10], although recent reports involving pooled analysis of Phase I patients suggest objective response rates between (7.2–9.4%) and a clinical benefit rate at 3 months of (48.2–53%).

At our Institution, patients (of adequate performance status) with advanced sarcoma who have no standard treatment options have traditionally been offered the possibility of participation in a Phase I clinical trial. We are unaware of any other study analysing the outcome and potential prognostic factors in sarcoma patients treated within Phase I clinical trials.

Patients and methods

This study included all consecutive sarcoma patients treated prospectively within Phase I trials in the Sarcoma and Drug Development Units at the Royal Marsden Hospital (RMH), from 1st August 1998 and 31st December 2009. From the hospital records, we selected only patients who met the following criteria: (1) histological confirmation by an experienced sarcoma pathologist; (2) first Phase I inclusion; (3) received at least 1 dose of the experimental agent. Several clinical parameters were collected at study entry, including sarcoma subtype, age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), full blood count, biochemistry (lactate dehydrogenase and albumin), number of metastatic sites, and prior oncology treatment, including the number of prior systemic therapies. Using these data, we derived the validated RMH prognostic score [11, 12]. All patients included in this analysis gave written informed consent for participation in a Phase I trial, and approval from the Royal Marsden Audit Committee was obtained prior to commencing this study.

Patient follow-up and response evaluation

From 2003 onwards, baseline tumour measurements were performed within 4 weeks of the first administration of study drug; between 1998 and 2002, patients had baseline measurements performed up to 8 weeks prior to first administration of study drug. Tumour measurements were repeated every 6–8 weeks during the first 6 months on trial. Tumour responses were confirmed retrospectively by a radiologist using Response Evaluation Criteria In Solid Tumours (RECIST) [13]. Toxicity and maximum grade were collected as originally recorded in the medical records, and when required, the clinical trial record. In all trials included in the present analysis, toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE), either version 2.0 or 3.0. Survival was obtained form the hospital medical records, and when necessary by contacting the general practitioner or referring institution.

Statistical methods

Overall survival (OS) was defined as the time between day 1 on Phase I trial and either the date of death or the last follow-up (if death was not observed during the follow-up period). For those patients with evaluable disease for response, progression-free survival time was defined by the time elapsed between day 1 on treatment until radiological progression or disease-related death (which ever occurred first), if no evidence of progression was documented at last follow-up, PFS was censored at the time of last radiological evaluation. Analysis of the effect of potential prognostic factors was undertaken using Cox's regression to determine the subset of baseline characteristics that provided independent prognostic information as continuous variables in our series. Subsequently, prior prognostic variables in the RMH score were categorised: elevated LDH (>ULN); low albumin (<35 g/L); and more than two sites of metastatic disease. Other numeric variables were categorised based on their deviation from standard reference. Median PFS and OS as well as their 95% confidence intervals were determined with the Kaplan–Meier method, and survival curves were compared with the logrank test. We calculated the RMH score based on each weighed equally: LDH normal (0) versus LDH > ULN (+1); albumin more than 35 g/L (0) versus albumin less than 35 g/L (+1); metastatic sites <2 (0) versus more than 2 (+1, see Table 1). The prognostic score for each individual was derived from the sum of these three

Table 1 Clinical characteristics of 133 patients treated within the Royal Marsden Drug Development Unit

Characteristics	Number (%)
Age (years)	
Median	48.0
Range	12.5–81.9
Gender	
Male	71 (53.4)
Female	62 (46.6)
Histological subtype	
Leiomyosarcoma	16 (12.0)
GIST	15 (11.3)
Liposarcoma	15 (11.3)
Chondrosarcoma	12 (9.0)
Synovial sarcoma	9 (6.8)
Fibrosarcoma	8 (6.0)
Osteosarcoma	5 (3.8)
MPNST	5 (3.8)
MFH	5 (3.8)
Solitary fibrous tumour	5 (3.8)
Alveolar soft part sarcoma	4 (3.0)
Other	24 (18.0)
Histological grading	
Low grade	27 (20.3)
Intermediate grade	40 (30.1)
High grade	37 (27.8)
Unknown/unclassified	29 (21.8)
Previous surgery	
Yes	112 (84.2)
No	21 (15.8)
Previous radiotherapy	
Yes	66 (49.6)
No	67 (50.4)
Previous systemic therapy	
0	7 (5.3)
1	33 (24.8)
2	26 (19.5)
3	35 (26.3)
4	18 (13.5)
5	9 (6.8)
6	5 (3.8)
Time from diagnosis to metastatic disease[a] (months)	
Median	15.5
Range	0–191.8
Time from metastatic disease to Phase I[a] (months)	
Median	18.6
Range	0.3–145.9
Drug class	
Antiangiogenic	43 (32.3)
IGF1-R/PI3K/mTOR/AKT pathway	30 (22.6)
Novel cytotoxic	16 (12.0)
DNA synthesis and repair	13 (9.8)
Growth factor receptor inhibitor	13 (9.8)
Cell cycle and apoptosis	9 (6.8)
Oxidative metabolism	6 (4.5)
Biological	3 (2.3)
Performance status	
0	37 (27.8)
1	89 (66.9)
2	7 (5.3)
RMH score	
0	20 (15.0)
1	57 (42.9)
2	31 (23.3)
3	25 (18.8)

[a] Fourteen patients did not have metastatic spread, but presented with locally advanced refractory/relapsing disease

components used in the prognostic model. All *P* values were 2 sided, and a significance level threshold of 0.05 was used. The analysis was performed using SPSS 15.0 (SPSS Inc., Chicago, Il).

Pathological tumour grade was included in the prognostic analysis, even though grading is not recommended for certain histological subtypes, such as GIST and extraskeletal chondrosarcoma, and for others such as malignant peripheral nerve sheath tumour, it is not regarded as of prognostic value [14, 15].

Results

Patient characteristics

One hundred and thirty-three sarcoma patients were treated within the Royal Marsden Sarcoma and Drug Development Units between 1st August 1998 and 31st December 2009. The clinical characteristics of these patients are summarised in Table 1 as well as the trial treatment administered. The median age of these patients was 48.0 years (12.5–81.9). There were 71 men and 62 women. The most common histological subtype was leiomyosarcoma ($n = 16$, 12.0%), followed by GIST and liposarcoma ($n = 15$, 11.3% each). One hundred and twelve (84.2%) had undergone previous surgery, and 66 (49.6%) had received prior radiotherapy. This series of patients had received a median of 3 (range 0–6) prior lines of systemic therapy, and 7 (5.3%) received treatment with in the Phase I Unit as their first-line systemic therapy. Thirty seven (27.8%) patients had a PS of 0, and 7

(5.3%) had a PS of 2. Twenty five (18.8%) patients had a RMH score of 3. The most frequently employed trial drugs were antiangiogenic agents ($n = 43$, 32.3%) followed by agents targeting the IGF1-R/PI3 K/mTOR/AKT pathway ($n = 30$, 22.6%).

Tumour response and tolerability

One hundred and twenty-seven patients were evaluable for response according to RECIST, and the other 6 were GIST patients who entered a trial of SR4554, an oxidoreductive agent and hypoxia marker, and were not evaluated for response and progression-free survival. One (0.8%) patient achieved a complete and 2 (1.6%) a partial response to treatment. These responses were observed in two patients with Ewing's sarcoma treated with IGF1-R inhibitors and a patient with alveolar soft part sarcoma treated with an antiangiogenic agent. Stable disease was recorded as the best response in 56 (44.1%) patients. Sixty-eight (53.5%) progressed on therapy at the first radiological evaluation. The median PFS was 2.1 months (95% CI; 1.7–2.5), and the median time to progression was 1.9 months (95% CI; 1.6–2.2). Kaplan–Meier curves of factors with a significant association with progression-free survival are shown in Fig. 1. The non-progression rate at 3 and 6 months was 31.5% (95% CI 23.4–39.6%) and 11.0% (95% CI 5.6–16.5%), respectively.

Twenty-four (18.0%) patients experienced grade 3 or 4 toxicity, and 16 (12.0%) stopped trial treatment due to

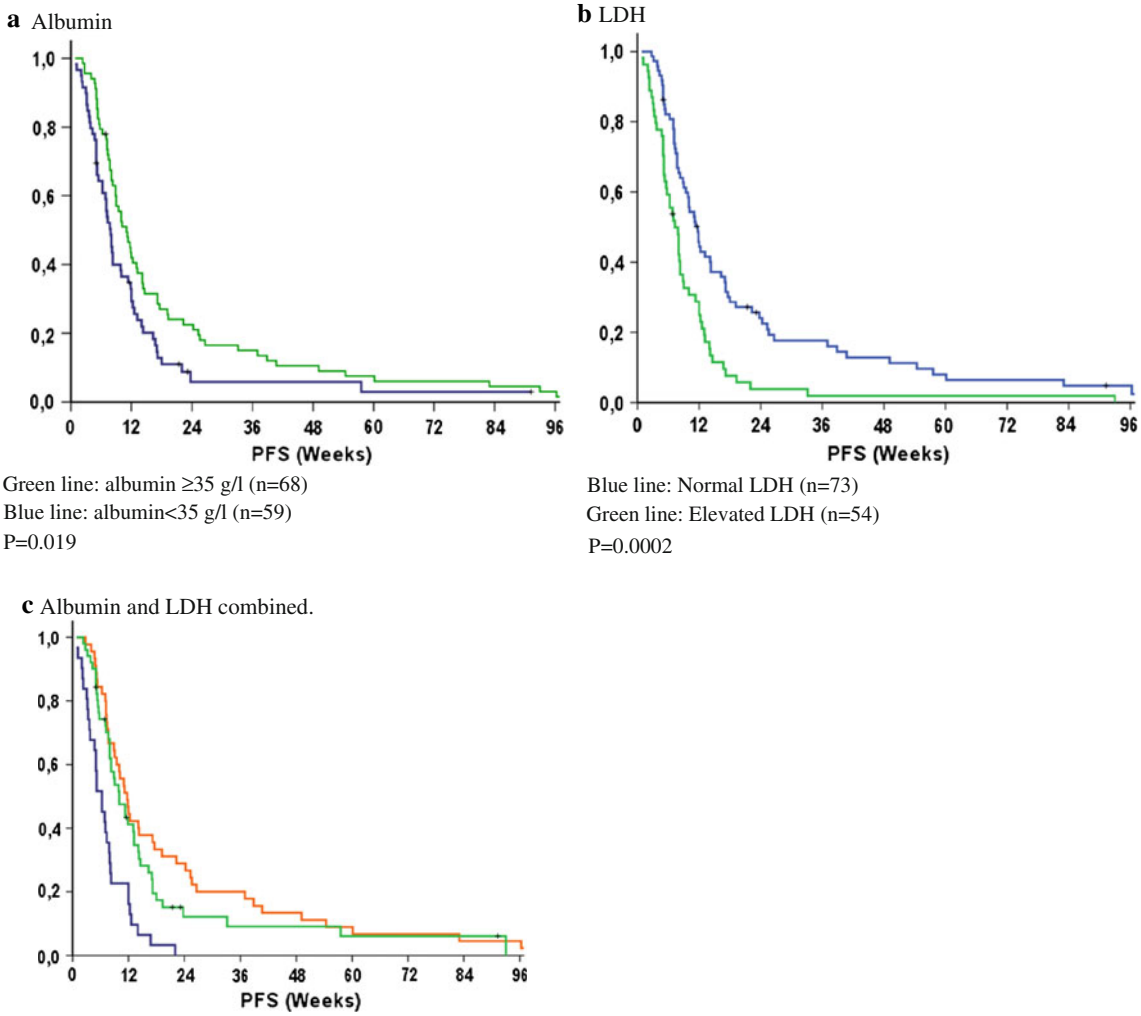

Fig. 1 Prognostic factors for progression-free survival in sarcoma patients ($n = 127$) treated within Phase I trials, **a** Albumin, *Green line* albumin ≥35 g/L ($n = 68$), *Blue line* albumin <35 g/L ($n = 59$), $P = 0.019$, **b** LDH, *Blue line*: Normal LDH ($n = 73$), *Green line* Elevated LDH ($n = 54$), $P = 0.0002$, **c** Albumin and LDH combined, *Red line* Normal LDH and albumin ≥35 g/L ($n = 45$), *Green line* Elevated LDH or albumin <35 g/L ($n = 51$), *Blue line* Elevated LDH and albumin <35 g/L ($n = 31$), $P = 0.000006$

toxicity. One hundred and four patients (78.2%) only received one Phase I trial, and 29 (21.8%) received further Phase I trials (ranging from 1 to 5 further Phase I trials). Thirty-four patients (25.6%) also received further systemic therapy following treatment within the Phase I Unit. Two of these patients were treated with both Phase I trials and non-Phase I agents. There were no treatment-related deaths.

Overall survival

The median overall survival was 7.6 months (95% CI 4.8–10.4), see Fig. 1b. The 6- and 12-month OS rates were 55.4% (95% CI; 46.8–64.0%) and 36.3% (95% CI; 27.9–44.7), respectively. The 90-day mortality rate was 16% (95% CI; 9.8–22.2).

Prognostic variables for OS are displayed in Table 2. Multivariate (MVA) analysis confirmed the independent prognostic value of serum albumin level (HR 0.89, CI 95% 0.85–0.92, $P = 0.0001$) and LDH (HR 1.72, CI 95% 1.35–2.20, $P = 0.0001$). PS and number of metastatic sites were both significant prognostic factors on univariate analysis, but failed to be significant independent factors on multivariate analysis.

The Kaplan–Meier analysis was used to further explore the prognostic value of these factors in our series, in which (1) patients with a low albumin (<35 g/dL) had a shorter OS compared to those with normal albumin (4.0 vs. 12.2 months, $P = 0.000002$); (2) patients with elevated LDH (>1*ULN) had a poor OS compared to those with normal LDH (4.3 vs. 11.6 months, $P = 0.001$); (3) patients with ≥3 metastatic sites have a shorter OS than those with less metastatic sites of disease (4.2 vs. 9.8 months, $P = 0.007$); and (4) Patients with worse performance status also presented with worse OS, (ECOG 2 [5.2 months] versus ECOG 1 [12.4 months] versus ECOG 0 [22.8 months], $P = 0.005$).

These three factors (albumin, LDH and number of metastatic sites) have been prospectively validated in the Phase I RMH score [12]. This score applied to our series identified patient groups with improved outcome: RMH score 0–1 (good prognosis) median OS 11.7 months (CI 95% 9.0–14.4) compared to those with worse RMH score (2–3), who had a median OS of 4.2 months (CI 95%3.3–5.1), $P = 0.003$. A Kaplan–Meier curve of overall survival according to Royal Marsden Score is shown in Fig. 2. Finally, we used a receiver operator curve (ROC) to estimate the ability of these three prognostic factors to predict the 90-day mortality in our series. The derived RCO curve had an area under the curve of 78% (CI 95% 67.5–88.5, $P = 0.00005$).

Discussion

Our study suggests that sarcoma patients with advanced disease resistant to conventional chemotherapy can derive clinical benefit from participation in Phase I trials. This is apparent despite the number of different experimental agents administered as well as the heterogeneous histological subtypes included in our study. We did not perform subgroup analysis according to histological subtype, as the number of patients in each subtype was too small to provide meaningful results.

Table 2 Univariate and multivariate analysis of prognostic factors for overall survival

Factor	Univariate analysis		Multivariate analysis	
	Significance *P* value	Hazard ratio (95% CI)	Significance *P* value	Hazard ratio (95% CI)
Age	0.89	1.00 (0.99–1.01)	NS	
Sex	0.45	1.16 (0.79–1.70)	NS	
Performance status			NS	
0	0.007			
1	0.009	1.82 (1.16–2.85)		
2	0.008	3.36 (1.37–8.24)		
Number previous lines of therapy	0.07	1.12 (0.99–1.26)	NS	
Histological grading[a]			NS	
Low	0.002			
Intermediate	0.704	1.12 (0.63–1.97)		
High	0.003	2.38 (1.34–4.25)		
Albumin	0.0001	0.89 (0.85–0.92)	0.0001	0.89 (0.85–0.92)
LDH	0.000004	1.72 (1.34–2.17)	0.0001	1.72 (1.35–2.20)
Number of metastatic sites	0.009	1.27 (1.06–1.53)	0.12	1.17 (0.96–1.42)

NS Not significant, *95% CI* 95% confidence interval

[a] Tumour grade at diagnosis not available in 29 patients

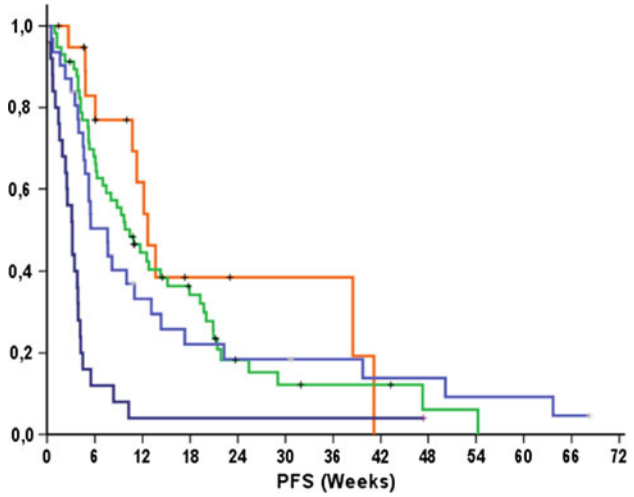

Fig. 2 Kaplan–Meier curve of overall survival according to Royal Marsden Score, *Red line* Score 0 (No adverse prognostic factors) ($n = 20$), *Green line* Score 1 (1 adverse prognostic factors) ($n = 57$), *Light blue line* Score 2 (2 adverse prognostic factors) ($n = 31$), *Dark blue line* Score 3 (3 adverse prognostic factors) ($n = 25$), $P = 0.0000001$

By definition, our series of patients were heavily pretreated, having received a median of 3 prior lines of systemic treatment in addition to surgery, radiotherapy or radiofrequency ablation. Furthermore, a previous analysis of all soft tissue sarcoma patients treated at the Royal Marsden Hospital between 1991 and 2005 demonstrated a median overall survival of 12 months following first-line chemotherapy [16] and 8 months following second-line chemotherapy [17] for metastatic/recurrent disease. The median overall survival of 7.6 months of our heterogeneous cohort of patients treated within the Phase I Unit compares favourably with these previous results. Currently, only an abstract presentation at the European Society of Medical Oncology Meeting in 2008 has reported the outcome of sarcoma patients treated within Phase I trials. This study consisted of a very small series (38 patients) and reported a median PFS of 2.7 months and a median OS of 9.2 months [10]. This study also reported a statistically significant difference in PFS (but not in OS) between patients treated with antiangiogenic agents and those treated with other agents. We did not observe a significant difference in PFS between antiangiogenic agents and those treated with drugs targeting the IGF1-R/PI3K/mTOR/AKT pathway and other Phase I drugs.

Although the objective response rate was low ($n = 3$, 2.3%) in our study, the non-progression rate of 31.5% at 3 months is encouraging in the context of dose-finding experimental trials. A retrospective analysis of 12 clinical trials performed by the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group suggested a 3-month progression-free rate of $\geq$40% would be indicative of drug activity in the second-line setting and that a 3-month progression-free rate of $\leq$20% would be indicative of drug inactivity [18]. Furthermore, patients with histological subtypes that are known to be chemo resistant (such as clear cell sarcoma [19]), could be offered Phase I entry early in the managementof metastatic disease.

The patients in this study tolerated treatment well, and only 16 (12.0%) stopped therapy due to toxicity. It was not possible to retrospectively ascertain the features of the grade 3/4 toxicity observed, i.e. whether this was due more to the characteristics of the individual patients or the Phase I drugs administered. It is also important to note that there were no treatment-related deaths. In addition, 28 (21.1%) received more than one Phase I trials. Thirty four (25.6%) patients were treated with systemic therapy (not Phase I trial) following participation in a Phase I trial.

We also found serum albumin and LDH to be independent prognostic factors for OS. Our study suggests that the RMH score could be of value in advising sarcoma patients of the potential value of Phase I trial entry.

In conclusion, our retrospective study showed that an unselected series of sarcoma patients derived clinical benefit from participation in Phase I trials, supporting the active recruitment of sarcoma patients into such trials, particularly if there is molecularly driven hypothesis for drug action. Such benefit is likely to increase with greater understanding of the biology of this complex group of diseases, and the identification of patients with particular molecular targets likely to respond to specific drugs.

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