ORIGINAL ARTICLE

Clinical outcomes and prognostic factors of patients with advanced mesothelioma treated in a phase I clinical trials unit

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Abstract

Background: We have previously reported a prognostic score for patients in phase I trials in the Drug Development Unit (DDU), treated at the Royal Marsden Hospital (RPS). The RPS is an objective tool used in patient selection for Phase I trials based on albumin, number of disease sites and LDH. Patients with mesothelioma are often entered to phase I trials as the disease remains localised for long periods of time. We have now reviewed the clinical outcomes of patients with relapsed malignant mesothelioma (MM) and propose a specific mesothelioma prognostic score (m-RPS) that can help identify patients who are most likely to benefit from early referral.

Methods: Patients who participated in 38 phase I trials between 09/2003-10/2015 were included in the analysis. Efficacy was assessed by response rate, median overall survival (OS) and progression-free survival (PFS). Univariate (UVA) and multivariate analysis (MVA) were carried out to develop the m-RPS.

Results: 65 patients with advanced MM were included in this retrospective study. PFS was 2.5 months (95% CI 2.0-3.1 months) and OS was 8 months (95% CI 5.6-9.8 months). Four (6%) patients had RECIST partial responses; 26 (40%) patients had RECIST stable disease >3 months. The m-RPS was developed comprising of 3 different prognostic factors: a neutrophil: lymphocyte ratio (NLR) greater than 3, the presence of more than 2 disease sites (including lymph nodes as a single site of disease) and albumin levels less than 35 from the MVA. Patients each received a score of 1 for the presence of each factor. Patients in group A (m-RPS 0-1; n=35) had a median OS of 13.4 months (95% CI 8.5 - 21.6), while those in group B (m-RPS 2-3; n=30) had a median OS of 4.0 months, (95% CI 2.9 - 7.1, p<0.0001). 56 (86%) patients experienced G1-2 toxicities, while reversible G3-4 toxicities were

observed in 18 (28%) patients. Only 10 (15%) patients discontinued phase I trials due to toxicity.

Conclusions: Phase I clinical trial therapies were well tolerated with early signals of antitumor activity in advanced MM patients. The m-RPS is a useful tool to assess MM patient suitability for phase I trials and should now be prospectively validated.

Background

The incidence of malignant mesothelioma (MM) is increasing, with an average of 14,200 MM cases diagnosed globally each year before a predicted plateau in 2020 [1]. Systemic treatment and radiotherapy aim to prolong survival and improve quality of life for patients presenting with advanced disease not amenable to radical therapy or those who have disease recurrence after surgical resection [2].

Platinum chemotherapy in combination with pemetrexed with or without bevacizumab is the preferred first-line treatment regimen for patients with advanced MM [3 4]. The overall survival with platinum-based doublet chemotherapy is approximately one year and patients who relapse more than 6 months after completion of initial chemotherapy may undergo re-challenge with a platinum-based regimen [3]. However, at current time, there are limited approved systemic treatment options for patients who relapse soon after first line therapy [5]. Single agent chemotherapy with vinorelbine or gemcitabine are typically used in the second or third line settings, but evidence supporting their effectiveness in advanced MM is limited to retrospective or modestly-sized non-randomised studies [6, 7].

Given the uncertain benefits of post first line chemotherapy, clinical trials including phase I studies, should be considered for patients who remain fit (e.g. Eastern Cooperative Oncology Group performance status [ECOG PS] 0-1) and keen to receive experimental therapies. Modern advances in drug discovery have led to the development of novel molecularly targeted inhibitors, immunotherapies and other antitumor agents, which may potentially be used in rational strategies that modulate the underlying pathogenesis of MM. For example, preclinical studies indicate that the phosphatidylinositol 3-kinase (PI3K) pathway is a key signalling trunk in MM, suggesting that critical points along this network are rational targets for therapeutic intervention [8]. Similarly, focal adhesion kinase (FAK) and histone deacetylase (HDAC) inhibitors have demonstrated promising activity in animal models of MM based on robust scientific rationale [9, 10].

Phase I clinical trials administered within a specialist clinical trials unit offer patients the opportunity to receive novel antitumor agents as single agents or in combination regimens before they are advanced through the different phases of clinical trials and approved by regulatory agencies, a process that may take several years to complete (www.fda.gov). We have previously developed the Royal Marsden Hospital prognostic score (RPS) based on objective clinical markers, as a tool for patient selection for phase I trial entry [11]. Most of these patients had multiple sites of disease while mesothelioma remains localized for most of its natural history.

In this study, we undertook a retrospective review of the clinical characteristics and treatment outcomes of all patients with advanced MM who were treated on phase I trials in the Drug Development Unit at the Royal Marsden Hospital, London, UK. We focused on the safety and efficacy of these experimental treatments to assess if they

are comparable alternatives to approved post-1st line chemotherapy options. We also sought to establish a prognostic score specifically for patients with MM to improve phase I trial patient selection and outcomes.

Patients and Methods

We undertook a retrospective analysis of all patients with advanced MM who were treated in our Phase I Drug Development Clinical Trials Unit at the Royal Marsden Hospital, Sutton, United Kingdom, between September 2003 and October 2015. This retrospective study was approved by the Royal Marsden NHS Foundation Trust Committee for Clinical Research. All patients had histologically confirmed MM reviewed by expert pathologists at The Royal Marsden or the referring local Institution and fulfilled the eligibility criteria of their allocated clinical trial. For patients who participated in more than one trial, their inclusion date for this retrospective study is the first day on their first trial. Patient data were obtained from the Royal Marsden Hospital electronic patient record system. Baseline patient clinical factors collected included age, gender, prior lines of treatment, best response to previous chemotherapy, ECOG PS, primary site, histological subtype, co-morbidities and smoking history.

Overall survival (OS) was defined as the time between treatment initiation in the first trial until date of death or time of their last follow up. Progression free survival (PFS) was defined as the length of time from commencing treatment within a phase I trial until the date of progression (clinical or radiological) or death while on trial. Modified RECIST criteria were used for all patients with pleural mesothelioma, while RECIST 1.1 criteria were used for patients with peritoneal mesothelioma. Radiological

imaging review was discussed in multi-disciplinary team meetings with a specialist radiologist. We sought to define a MM-specific RPS (m-RPS), by assessing baseline patient clinical factors in univariate (UVA) and multivariate analyses (MVA), respectively. In the MVA, we used a full model approach, which was constructed using those baseline patient clinical factors found to be significant in the univariate analysis. The STATA Program (Version 13.0) was used to carry out the statistical analysis. The Kaplan-Meier method was applied to examine PFS and OS, respectively. The Log-rank test was used to compare survival distributions. The cox proportional hazards regression model was used to estimate the hazard ratio (HR) for each factor; All P-values presented are two sided.

Results

Baseline characteristics

A total of 65 patients with advanced MM treated in 38 different Phase I trials at the Royal Marsden Hospital Drug Development Unit between September 2003 and October 2015 were included in the analysis. Only one trial involved a phase Ib cohort expansion study. Eleven patients participated in two consecutive phase I trials and one patient participated in four phase I trials. Baseline characteristics are shown in **Table 1**. The median age of patients at the start of their phase I trial was 64 years (range: 25-78 years); Sixty-one patients had pleural MM and in 49 cases it was of epithelioid histologic subtype. 37 (57%) patients had at least one comorbidity, with the most common being hypertension (n=20, 31%), vascular disease (n=7, 11%) and diabetes mellitus (n=5, 8%). All patients had an ECOG PS of 0-1 at phase I trial study entry.

Prior to participating in a phase I trial, the median number of lines of treatment received was 2 (range: 0-6 lines); 64 patients received at least one line of platinum-based chemotherapy; one patient elected not to receive 1st line chemotherapy. Twenty-five (38%) patients were rechallenged with platinum-based therapy, while 22 (34%) patients had vinorelbine chemotherapy prior to a phase I trial.

Phase I trial treatments and patient outcomes

Nine (14%) patients received chemotherapy in combination with a phase I trial agent. Twenty-eight (43%) and 12 (18%) patients received a PI3K pathway targeting agent or a histone deacetylase (HDAC) inhibitor, respectively. **Table 2** details the target and the class of phase I trial agents used in these clinical studies.

Overall, 4 (6%) patients had confirmed RECIST partial responses (to single agent PI3K pathway inhibitors [n=2], aurora kinase A inhibitor [n=1] and immune checkpoint inhibitor [n=1]); 26 (40%) patients had RECIST stable disease >3 months. The OS and PFS for the overall study population were 8.0 months (95% CI: 5.6-9.8 months) and 2.5 months (95% CI: 2.0-3.1 months), respectively. Patients who received a PI3K pathway inhibitor had a trend toward improved OS compared to the rest of the patient population who received other antitumor agents (median survival: 12.2 vs. 7.1 months, P=0.29), although PFS was similar (median survival: 2.8 vs. 2.5 months, P=0.93) **(Figure 1).**

Ten (15%) patients discontinued trial treatment because of drug-associated toxicities, while 3 (5%) subjects stopped due to patient choice for non-drug-related reasons. There were no deaths attributed to the investigational agent; one patient

died due to a lower respiratory tract infection having been on a PI3K pathway inhibitor trial for 8 weeks, which was deemed not to be related to the study drug. Overall, phase I trial treatments were well tolerated; 56 (86%) patients experienced G1-2 treatment-related toxicities, while G3-4 toxicities were observed in 18 (28%) patients. The most common G1-2 toxicities were fatigue (n=29, 45%), nausea and vomiting (n=19, 29%), chest wall pain (n=16, 25%), mucositis (n=12, 18%), dyspnea (n=11, 17%), loss of appetite (n=10, 15%) and rash (n=9, 14%). G3-4 toxicities included nausea (n=4, 6%), dyspnea (n=3, 5%), fatigue (n=3, 5%), anaphylaxis (n=1, 2%), pneumonitis (n=1, 2%), rash (n=1, 2%), hyperglycemia (n=1, 2%), chest wall pain (n=1, 2%), back pain (n=1, 2%), neutropenia (n=1, 2%) and thrombocytopenia (n=1, 2%).

Univariate and multivariate analyses

In the UVA for PFS, having a diagnosis of peritoneal MM, having two or fewer sites of disease, the absence of lymph nodes but not the neutrophil:lymphocyte ratio (NLR), were associated with improved PFS in our series of patients **(Appendix, Table 1)**. The UVA for OS showed that the female gender, having a diagnosis of peritoneal MM, previously receiving more than 1 prior line of chemotherapy, the presence of two or fewer sites of disease, the absence of lymph nodes, having albumin levels of at least 35, and a neutrophil-lymphocyte ratio (NLR) of less than 3 were associated with improved OS **(Appendix, Table 2)**.

Subsequently, in the MVA that was constructed using the significant univariate variables, the presence of lymph nodes at baseline emerged as an independent prognostic factor for reduced PFS (HR: 3.12, 95% CI: 1.7-5.8, P<0.001), while

having received more than 2 lines of treatment prior to participating in phase I trials was associated with prolonged PFS (HR: 0.5, 95% CI: 0.3–0.9, P=0.028) **(Table 3).** Having a NLR greater than 3, the presence of pathologically enlarged lymph nodes and the presence of more than 2 sites of disease at baseline were associated with poor overall survival (HR: 2.1, 95% CI: 1.0–4.2, P=0.048; HR: 2.3, 95% CI: 1.1-4.6, P=0.024; HR: 4.0, 95% CI: 1.7-9.2, P=0.001, respectively). Having serum albumin levels of at least 35g/L (HR: 0.3, 95% CI: 0.1-0.6, P=0.001), previously receiving more than 2 lines of treatment prior to a phase I trial (HR: 0.3, 95% CI: 0.2-0.6, P<0.001) and the best response of RECIST PR or SD to first line chemotherapy (HR: 0.3, 95% CI: 0.1-0.8, P=0.019) were all associated with increased OS **(Table 4).**

MM-specific RMH Prognostic Score (m-RPS)

We subsequently sought to define a m-RPS by assessing baseline patient factors that were found to be significantly associated with OS in the MVA **(Table 5)**. Therefore, a m-RPS comprising 3 different prognostic factors was developed, including a NLR greater than 3, the presence of more than 2 disease sites (including the presence of pathologically enlarged lymph nodes as a single disease site) and albumin levels less than 35g/L; each receiving a m-RPS score of 1 if present. These factors have previously been found to be prognostic in separate studies involving patients participating in phase I clinical studies, but have never been considered together in the context of a prognostic score [11, 12]. All three factors assessed objective data at treatment baseline and reflect the disease state of the individual patient.

We elected not to include 'response to first line chemotherapy' in our prognostic model since cancers may accumulate genomic and epigenetic events that alter the genomic composition of the original tumor that dictated its initial response to chemotherapy. Similarly, the number of prior lines of chemotherapy received by patients is subjective and is dependent on the preferences of the patient and referring oncologist. The 'number of disease sites' was selected as a factor for the m-RPS rather than the 'presence of pathologically enlarged lymph nodes' because it was a statistically stronger prognostic factor in the MVA. Unlike the original RPS, LDH was not significant in the MVA.

Accordingly, by applying this m-RPS to our patient population, patients were divided into two groups; group A: those with a good prognosis (n=35, m-RPS 0-1) and group

B: those with a poor prognosis (n=30, m-RPS 2-3). The median OS was 13.4 months (95% CI: 8.5-21.6) for group A, and 4.0 months (95% CI 2.9-7.1) in group B, P<0.0001 **(Figure 2)**. No patients in group A died within 90 days from the start of the trial, whereas the 90-day mortality rate was 33% (10/30 patients) in group B. This is an important factor since a life expectancy > 90 days is a common inclusion criteria for phase I trials. Of note, 5 of 6 patients with an m-RPS of 3 died within 90 days of treatment initiation, supporting the prognostic value of the m-RPS in patients with advanced MM referred for phase I trial consideration.

Discussion

The main objectives of a phase I clinical trial are the assessment of safety and tolerability, as well as the establishment of a recommended phase 2 dose schedule for the future development of novel anticancer agents [13, 14]. Patients with relapsed MM gain limited therapeutic benefit from conventional treatment options after first line platinum-based chemotherapy and may therefore, be considered for phase I trials if fit [5-7]. The OS of 8.0 months and the PFS of 2.5 months described in this retrospective series are comparable to the survival data reported in published studies describing the use of single agent chemotherapy in relapsed MM (OS range 4.9–9.6 months; PFS 1.6-1.7 months suggesting that phase I trials are a reasonable alternative to second line chemotherapy [5-7].

Importantly, these phase I trial agents were well tolerated, with mainly G1-2 toxicities observed, such as fatigue, nausea and mucositis. The frequency of G3-4 adverse events of 28% was comparable with previously reported data from larger datasets of patients with solid tumors participating in phase I studies and were importantly fully

reversible upon dose interruption or discontinuation [15, 16]. Of note, Raphael and colleagues described a higher rate of G3-4 toxicity, possibly because patients with ECOG PS2 were included in their analysis; A performance status of ECOG PS2 has previously been identified to be predictive for the onset of G3 or worse toxicity [16, 17]. There was no drug-related death in our series of patients which did not include PS 2, which is consistent with the low mortality rate (~0.5%) reported in other analyses of mortality in phase I oncology programmes [13, 14, 17].

Although 26 (40%) patients in our study had a best response of RECIST SD lasting greater than 3 months, it is possible that this was confounded by slowly progressing MM in these patients. In our study, patients were not 'molecularly matched' to targeted therapies and not unexpectedly, only a modest number of patients gained clinical benefit. In future, patient selection will be central to improving the number of patients that benefit from molecularly targeted agents in phase I trials. For example, the increased use of next-generation sequencing (NGS) technologies in the clinic has enhanced our understanding of changes that occur at a molecular level and may aid in the matching of advanced MM patients with novel therapeutics to optimise benefit from Phase I trial therapies [8].

Anecdotal examples of RECIST partial responses were observed in patients treated in our series of patients with novel PI3K pathway (n=2), aurora kinase (n=1) and immune checkpoint inhibitors (n=1). None of these classes of drugs would have been available to these patients outside these early phase clinical trials. These preliminary antitumor responses thus support the referral of such patients for consideration of novel agents given within the context of phase I clinical trials in

dedicated drug development units, and demonstrates the utility of these studies for preliminary antitumor efficacy signal searching in different tumor types including mesothelioma.

While the molecular characterisation of patients may contribute to the selection of patients more likely to benefit from a phase I trial, it does not aid in the prognostic determination of patient mortality within the first 3 months of trial treatment. Such a predicted life expectancy of 3 months is a key inclusion criteria of phase I clinical trials, but is challenging to predict. Since its validation in a prospective study, the RPS has been incorporated in the selection process of patients with advanced solid tumors for phase I trials [11]. An important limitation of the RPS is that given the pattern of disease spread in advanced MM, it cannot be reliably applied to this group of patients. Our MM-specific m-RPS was developed from baseline factors that significantly correlated with OS in a MVA. Patients with a m-RPS of 0-1 are suitable candidates for phase I trials as there were no deaths recorded in this group within 90 days of study initiation. This is in contrast to patients with an m-RPS of 2-3 who had a 90-day mortality rate of 33%. Furthermore, 5 of 6 patients with an m-RPS of 3 died within 90 days of treatment initiation, thus representing a patient population with very poor life expectancy with limited chances of benefit from a phase I trial. This scoring system now needs to be prospectively validated to serve as a clinical tool to aid in the selection of patients with MM referred for participation on phase I clinical trials. It may also be possible that the m-RPS could be of use as a prognostic tool in other treatment settings in advanced MM, for example in second or third line MM clinical trials, where an estimated prognosis of more than 3 months is often a mandatory entry criterion.

Patients with relapsed MM have limited treatment options and based on our data and other studies, phase I trials represent bona fide options, which are associated with potential clinical benefit and acceptable toxicities [17]. Since the identification of molecular pathways implicated in the oncogenesis of MM and the development of novel therapies that target such critical targets, the process of allocating patients to suitable trials is likely to become increasingly biology-driven. A MM-specific, validated prognostic tool, such as the m-RPS developed in this study, will also aid in the optimal selection of patients with advanced MM for participation in phase I clinical trials, and minimise the inclusion of individuals who are unlikely to remain on study for a sufficient duration of time to derive any potential meaningful benefit.

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Table 1. Baseline characteristics

Median age	64 years (range 25-78 years)
Gender	Male: 43 Female: 22
Median lines of treatment pre phase I	2 (range 1-6)
Best response to first line chemotherapy	PR: 22 SD: 35 PD: 7 NA: 1
Number of patients that had platinum re-challenge	25
Number of patients that had vinorelbine	22
Mean PFS after first line chemotherapy	8.1 months
Lines of treatment with a phase I trial	1: 53 2: 11 4: 1
ECOG PS	PS 0: 5 PS 1: 60
Primary site	Pleura: 61 Peritoneal: 4
Histological type	Epithelioid: 49 Biphasic: 4 Sarcomatoid: 2 Unknown: 10
Number of co-morbidities	≤2: 56 >2: 9
Type of co-morbidities	Hypertension: 20 Vascular: 7 Diabetes mellitus: 5
Smoking history:	Yes: 6

	Ex-smoker: 18 No: 16 Unknown: 25

Table 2. List of phase I studies classified by target class and target

Target class	Target	Number of patients
Cytoplasmic signalling protein	PI3K pathway	28
	IGF	4
	VEGF	1
	Pan-HER family	1
	AGC kinase	1
DNA repair and Antisense	HDAC	12
	PARP	4
	ATR	4
	Aurora A	3
Cytotoxic	Microtubule	1
	Alpha folate receptor	1
	Nucleoside analogue	2
Other	Oleic acid analogue	1
	Immune checkpoints	4
	Apoptosis	2
	MCT-1	1
	Chemotherapy combination	9

PI3K: Phosphoinositide 3-kinase; IGF: Insulin-like growth factor 1; VEGF: Vascular endothelial growth factor; HER: human epidermal growth factor receptor; AGC: protein kinase A, G, and C families; HDAC: Histone deacetylase; PARP: Poly ADP ribose polymerase; ATR: ataxia telangiectasia and Rad3-related protein; MCT-1: Monocarboxylate transporter 1

Table 3: Multiple regression analysis – multivariate analysis for PFS

Variable	HR	95% CI for HR	Cox PH test
Lymph nodes - Yes	3.12	1.70 – 5.75	0.000
What line of treatment phase 1 - >2	0.53	0.30 – 0.93	0.028
Constructed using significant univariate models (n=62) Progression free survival (p<0.05)			

Table 4: Multiple regression analysis – multivariate analysis for OS

Variable	HR	95% CI for HR	Cox PH test
NL ratio - >3	2.06	1.01 – 4.23	0.048
Lymph Nodes - Yes	2.26	1.11 – 4.61	0.024
Number of metastatic sites > 2	3.97	1.71 – 9.20	0.001
Albumin≥35	0.29	0.14 – 0.59	0.001
>2 prior lines of treatment	0.30	0.15 – 0.59	0.000
Best response to first line chemo – PR & SD	0.29	0.11 – 0.82	0.019
Overall survival (P<0.005) Constructed using significant univariate models (n=61)			

Table 5. RPS and m-RPS

RPS		m-RPS	
Variable	**score**	**Variable**	**score**
Low albumin (<35 g/dL)	+1	Low albumin (<35 g/dL)	+1
Elevated LDH (>1XULN)	+1	NLR > 3	+1
Number of metastatic sites > 2	+1	Number of sites of disease >2	+1
Categories	**score**	**Categories**	**score**
Good prognosis	0-1	Good prognosis	0-1
Poor prognosis	2-3	Poor prognosis	2-3

Figure 1. Overall survival in patients treated on a PI3K inhibitor-based trial versus patients treated with a non-PI3K inhibitor based trial

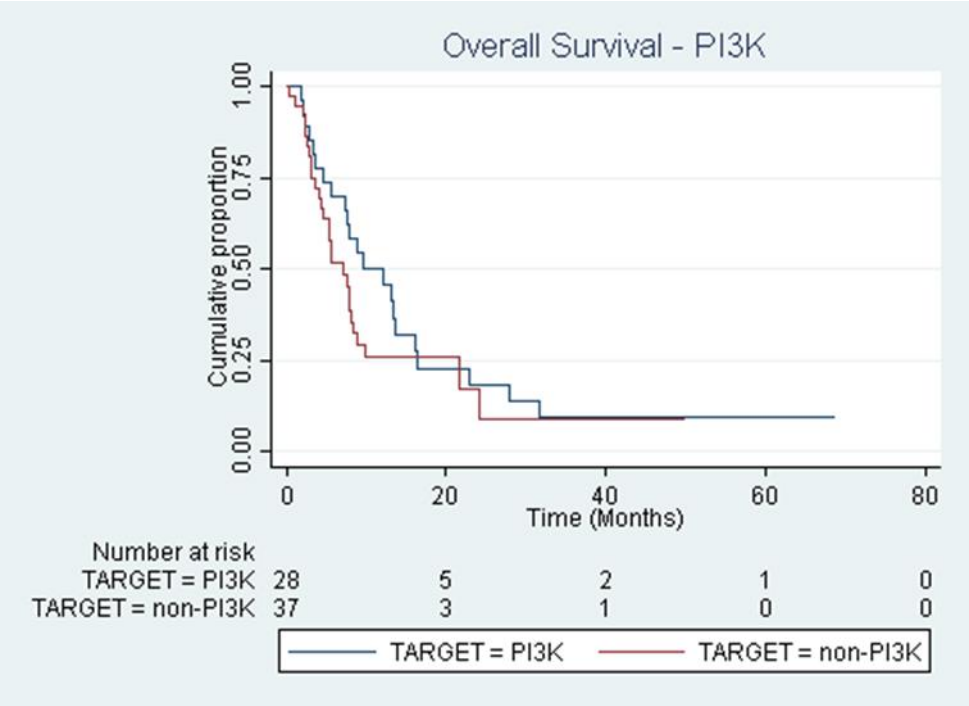

Figure 2. Overall survival in group A (progcat 1) and group B (progcat 2)