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Identification of factors limiting patient recruitment into phase I trials: A study from the Royal Marsden Hospital

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ABSTRACT

Aim: To identify factors that may prevent or delay patients referred for consideration of phase I studies from commencing such a study.

Methods: A retrospective audit of phase I study referrals for the period 1st March to 31st August 2005 to the Drug Development Unit was performed. All reasons that led to either delay or recruitment failure were documented and analysed.

Results: Data from 176 patients (105M/71F) were analysed. Median age at referral was 59 years and median performance status (PS) was 1. Of these, 56 (32%) were successfully recruited in a phase I trial. The median time from trial allocation to commencement of treatment was 4.8 weeks. Poor or deteriorating PS was the reason for delay or recruitment failure in 43 (35%) of non-recruited patients.

Conclusions: Poor or deteriorating PS was the most common factor limiting accrual to phase I trials. Better patients' selection on this basis might improve recruitment rates.

1. Introduction

Phase I trials are the first step in clinical drug development and are primarily designed to evaluate the safety of new agents, including antineoplastic drugs. Phase I trials in cancer should determine the toxicity, the maximum tolerated dose, the recommended dose for further evaluation and the pharmacokinetics of either a new agent or a new combination or schedule.[1,2] Recent advances in the molecular biology of malignant tumours have led to a better understanding of several pathways implicated in the tumour growth process and have highlighted these steps as potential targets for anticancer treatments. Examples include the PI3K/AKT/mTOR pathway, the RAS/RAF/MEK/ERK pathway and EGFR and VEGF-R signalling pathways. In this context, phase I trials are critical for the development of new, target-based, more effective and safer therapies.[3,4]

Although clinical trials are a crucial step in the development of new cancer treatments, their progress can be limited by low accrual rates.[5] Oncology patients who have been referred to the phase I trials clinic represent a unique but heterogeneous subset of patients who have usually exhausted standard treatment options, but still may continue to be functionally well. Nevertheless, the risks associated with an investigational drug are unknown and the likelihood of therapeutic response is generally low or at least uncertain.[6] Several factors may be responsible for patients not participating in a phase I trial. In a recently published study from Princess Margaret Hospital in Canada, performance status, significant abnormalities in biochemical and/or haematological parameters and

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rapid disease progression were found to be the most common limiting factors for enrolment of patients in phase I trials.[7]

The identification of barriers to participation in phase I trials could be useful in order to improve the recruitment of patients with advanced malignancies into early phase trials. We therefore conducted an internal analysis, focusing on the first 6 months of the newly opened Drug Development Unit at the Royal Marsden Hospital. In order to improve patient selection and guide the referral of patients to phase I centres, this study aims to analyse in a single institution the clinical and demographic features, which influence the recruitment of patients to phase I trials.

2. Materials and methods

This was a retrospective audit of clinical trial phase I study referrals for the period 1st March to 31st August 2005. It had received full approval from the Hospital's Audit Committee. The Drug Development Unit is located in the Southern part of London and patient referrals for phase I studies come primarily from the specific oncology units in the Royal Marsden Hospital and through the network of oncology consultants in the South East of England.

Clinical notes and information from the hospital's database were examined for consecutive referrals during this six month period.

The Drug Development Unit Guidelines (Standard Operating Procedures), which are listed below, were followed.

(1) The referral letter to the DDU is read by a consultant.
(2) The patient is seen in clinic on the next available date for a general discussion and assessment, where the general concept of clinical trials is described to the patient by a member of DDU staff prior to discussion of specific trials. Performance status is assessed in this first visit and baseline blood work is obtained.
(3) Patients that are potentially suitable for phase I trials are provided with a generic phase I information sheet. Those not suitable are referred on or back to the original referring physician.
(4) On a weekly basis, and within 2 working days of the first visit, the DDU holds a patient allocation meeting (PAM) at which the suitability of patients on the eligible patient list for any particular trial is discussed.
(5) Suitable patients are allocated to a trial according to the availability of slots or they remain on the eligible patient list for discussion at the next PAM if a slot is not available.
(6) Patients allocated to a trial are added to a waiting list for that particular trial and attend a further clinical assessment to confirm eligibility criteria. Patients will not be assigned to a waiting list for a trial that has no available slots within the next 6 weeks.
(7) Patients that are ineligible or are not wishing to participate in any clinical trial are referred on or back to the referring physician.
(8) Patients meeting the trial specific criteria are lined up for the trial and are regularly reviewed for eligibility until commencing the trial. During this period some of them become ineligible and are managed accordingly.
(9) Patients that continue to meet the criteria are placed on the trial.

An overall period of 4 weeks from the date of the first visit to the date of treatment commencement has been considered by the Unit as acceptable, given the constraints of forward planning required for phase I trials. Any period significantly longer than 4 weeks is considered a treatment delay.

Demographic data including gender, age, residence and referral site were recorded. Clinico-pathological characteristics of the primary tumour including tumour type, metastatic status and number and type of previous treatments were also collected. Moreover, Eastern Cooperative Group (ECOG) performance status (PS) was recorded. In those cases where the outcome of referral was that the patient was not enrolled into a phase I trial, the date and reason for the decision were recorded.

3. Results

A total of 187 patients were referred between February and August 2005. Four were excluded as they participated instead in phase II clinical trials and seven were never seen in phase I unit for unknown reasons. Hence, 176 cases (105 males, 71 females) with a median age of 59 years (range 19–78) were eligible for analysis. Median PS at first visit was 1 (range 0–3).

A total of 53% were referred internally from other units of Royal Marsden Hospital. Details of tumour type, disease spread and prior therapy are given in Table 1. The median interval from referral to first visit in the DDU was 2.1 weeks for internal referrals and 2.4 weeks for outside referrals. Ten referred (5.7%) were first seen on the day of referral – all from the RMH.

Fifty-two per cent (52%) had single organ metastatic disease whereas the rest had multiple organ involvement. Regarding previous conventional treatment 32 patients were chemotherapy naïve, 19 had one line of treatment, 49 had two, 56 had three and 50 had four or more lines of treatment. Eighty-five patients had also previous radiotherapy (RT) in several sites of the skeleton as part of the standard care.

Only 2 patients (1%) had no metastatic locations recorded. Just over half of all referrals had a single site recorded (91, 51.7%), just under a third had two sites recorded (57, 32.4%) and just over a tenth had three sites recorded (21, 11.9%). The proportion of patients in the recruited and non-recruited groups with one, two or three metastatic sites was very similar (50%, 30% and 10%, respectively). Almost one-third of patients (32%) had three previous lines of treatment and over a quarter (28%) had two previous lines. Eleven per cent of patients had one or four lines of previous treatment. Thirty patients (17%) had more than four previous lines of treatment. Two patients (who were not subsequently recruited into a trial) had no previous lines of treatment.

Just over half of referred patients (52%) had no previous RT. Of the 85 (48%) who did, just over a third (31, 36%) had pelvic RT. No other major sites of RT were identifiable.

Table 1 – Patient's demographics

Characteristics	Total (%) 176	Recruited 56 (31.8)	Not recruited 120 (68.2)
Median age	58.7	58	59
PS			
0	31 (17.6)	15	16
1	72 (40.9)	27	45
2	23 (13.1)	3	20
3	11 (6.2)	0	11
Not documented	39 (22.2)	11	28
Tumour types			
Urology	54 (30.7)	19	35
Sarcoma	22 (12)	8	14
Gynaecology	21 (11.9)	7	14
GI	32 (17.1)	8	24
Breast	17 (9.7)	3	14
Lung	14 (8)	3	11
Melanoma	5 (2.8)	0	5
Unknown primary	4 (2.3)	2	2
Head and neck	4 (2.3)	3	1
Others	3 (2.1)	2	1
Previous lines of chemo			
Naïve[a]	32 (18)	11	21
1	9 (5)	3	6
2	29 (16.5)	12	17
3	56 (31.8)	12	44
>3	50 (28.5)	18	32
Number of metastatic sites			
0	2 (1.1)	0	2
1	91 (51.7)	31	60
2	57 (32.4)	17	40
⩾3	24 (13.6)	7	17
Previous RT			
No	91 (51.7)	31	60
Yes	85 (48.3)	25	60

a The majority of chemotherapy naïve patients are those with hormone refractory prostate cancer patients who entered in taxotere based phase I programmes, as taxotere was not licensed in UK for this disease at that time.

Table 2 – Clinical trials allocated at first meeting

Clinical trials	Total allocated	Allocated, recruited	Allocated, not recruited
Tyrosine kinase inhibitors VEGF FGFR EGFR IGFR 1 EGFR/HER2 FGFR	31	13	18
TKI plus chemotherapy	13	8	5
Monoclonal AB (MAB)	6	6	0
MAB plus chemotherapy	4	2	2
PARP inhibitor	8	1	7
Histone deacetylase inhibitors (HDAC)	4	3	1
Virus	6	5	1
Virus plus radiotherapy	1	1	0
Novel cytotoxic agents	8	2	6
Others	21	13	8
Total	105	56	49

3.1. *Clinical trials allocated*

Clinical trial allocation took place for 105 patients, 58% of those referred. The largest number of patients allocated to one trial was 13 [to an IGF-1R monoclonal antibody + Docetaxel], of whom 8 (55%) were subsequently recruited. At the time of analysis, 22 trials were actively recruiting patients. A broad spectrum of novel target agents was represented either as single agents or in combinations (Table 2).

3.2. *Recruitment failure and delay*

From the total of 176 new referred patients, 56 (32%) were successfully recruited into a phase I trial. The highest proportion of patients not recruited (85, 71%) failed at review of first visit or at the patients allocation meeting, which takes place two days after. Of these, 28 had a deteriorating PS, 29 had other treatment available and 8 refused treatment. A further 20% of non-recruited patients failed at second visit, of which 10 patients failed due to deteriorating PS. Overall, 43 (35%) of non-recruited patients failed due to deteriorating PS and 30 (23.3%) failed because there was another treatment available. A further 13 patients declined treatment because of the uncertainty of the outcome. Thirteen patients failed recruitment due to abnormal liver or renal function test results, 8 failed as they did not have disease progression and 4 (3%) developed brain metastases. Only 2 patients failed recruitment due to travel distance, 1 due to no suitable trial slot and 1 due to sustained myelosuppression most likely attributed to malignant bone marrow infiltration. A very small number of patients failed recruitment due to a combination of these reasons (Table 3). There was no difference in, age, the number of metastatic sites and the number of previous lines of treatment in recruited and non-recruited patients.

3.3. *Reasons for delay in admission*

Just over half of all patients (31, 55.3%) began treatment within 4 weeks of the allocation meeting, which was the target time. Of the remaining 25 (44.6%) patients with delays in this period, the majority (16, 64%) were patient-related, including 6 for medical reasons (e.g. having treatment for an active infection, abnormal liver function and borderline PS) and 4 for patient holidays. Treatment-related reasons included immediate slot unavailability in two cases and 4 patients needed a minimum wash out period before starting a phase I trial. One patient was delayed because there was not a side room available for a 5-days treatment. The reasons for delay in starting treatment are described in Table 4.

Table 3 – Recruitment failure summary

Stage	Review 1st visit and PAM	2nd visit	Consent visit	Screening visit	Total
Number of points failed (%)	85 (71)	24 (20)	1 (0.8)	10 (8.3)	120 (100)
Medical reasons					
Deteriorating PS	28	10	0	5	43
Other treatment available	29	1	0	0	30
Co morbidity factors	4	4	0	3	11
Abnormal blood tests	9	2	1	1	13
Not progressing	5	2	0	1	8
Non-medical reasons					
Travel/distance	2	0	0	0	2
Patient refusal	8	0	0	0	13

Table 4 – Phase 1 trial admission summary – recruited patients, reasons for delay in admission

	Delay of more than 4 weeks between allocation and 1st treatment	
	Not delayed over 4 weeks	Delay > 4 weeks
No. of patients recruited (%)	31 (55.3)	25 (44.6)
Reasons for delay		
Patient related		15 (64%)
Medical issues/PS		6
Holiday/patient decision		5
Not clear reason		3
Disease progression		1
Treatment related		6 (20%)
Slot availability		2
Washout from previous treatment		4
Unit related		1 (4%)
Availability of single room		1
Not clear/not specified[a]		3 (12%)

a Reasons for delays in treatment for 2 of the 3 remaining patients were due to the timing of visits in relation to bank holidays.

3.4. *Median time in the different recruitment steps*

The median interval from referral date to first hospital visit was 2 weeks. There was no significant difference between internal referrals and patients who were referred from outside the Royal Marsden Hospital. This was also similar for both recruited and non-recruited patients.

For patients who were finally recruited in a phase I trial, the median time from referral to admission was 7.5 weeks, from visit 1 to admission was 5.6 weeks, whereas from allocation to admission was 4.8 weeks.

4. Discussion

In our study, we found that the success rate in recruiting patients to phase I trials was 32%. This means that one out of three patients who are referred will eventually enrol on a phase I programme. By comparison, a recently published similar study from Princess Margaret Hospital in Canada showed that of a total of 667 new referrals to the phase I clinic in a period of 5 years, the overall accrual rate was 29.5%, a remarkably similar figure [7].

Medical issues limited accrual in the majority of patients. The main reason for precluding patients from entering a phase I trial was PS throughout the different steps in the recruitment process, followed by the availability of further conventional management. Less common medical factors were ineligibility due to abnormal liver and kidney function and the presence of previously unrecognised brain metastases. Interestingly, 8 patients were not allocated in a trial because there was no evidence of disease progression upon referral.

The main non-medical reason responsible for not recruiting patients was the uncertainty of benefit and concern about toxicity. Similar results were reported from the Canadian group.[7] They also report that 8.4% were due to a lack of trial slots. In our study, only 1 patient was not allocated into a phase I trial because of slot unavailability. We believe that the fact that more than 20 trials were active minimises the prospect of slot unavailability. Travel distance was not a significant deterrent to entry, as the majority of patients were resident within 1–2 h travel distance from the Unit.

Previous studies have reported significantly lower recruitment rates within oncology trials. Corrie et al. analysed the factors limiting the recruitment of 1411 patients into phase I–III oncology trials at the West Anglia cancer research network in the United Kingdom.[8] Although their overall recruitment rate was 19%, no trials were available for 40% of patients, 32% of patients were ineligible and 19% of eligible patients declined entry into a study. Another smaller study by Lara et al. at the University of California Davis Cancer Center in the United States prospectively assessed patient accrual into phase I–III oncology trials and reported an accrual rate of 14% out of 276 patients. Thirty-seven patients or 49% of those they considered eligible for available protocols refused to participate for reasons including a desire for other treatment, distance from the cancer centre and insurance denial.[9]

Specific patient factors have been reported to influence the eligibility and the accrual in phase I trials. The Canadian group found that age and extent of prior therapy were significantly negative factors.[7] In our study, however, neither age nor tumour type nor previous lines of chemotherapy were

associated with limited accrual in our phase I trials. PS was the only factor that limited accrual through the different steps in a phase I process.

The median time between a patient's referral to the unit and admission to a phase I trial was 7.5 weeks and from trial allocation to trial entry was 4.8 weeks. These time intervals have given grounds for concern and have led to internal reorganisation, in order to maximize the use of available slots. The Canadian group reported a lower period with the majority of their patients being treated within a month from the initial unit visit with a median of 2.4 weeks.

At present, our Unit's Standard Operating Procedures state that a 4 weeks interval between the initial visit and start on a phase I trial is acceptable. During that time, the patient will be allocated to a specific trial, will have enough time to read carefully the patient information sheet, will be consented, screened and have the entire necessary baseline investigations performed. Our study indicates this goal has been achieved in just over half of the patients and further internal reorganisation is now in place to increase this proportion.

A key question is whether a significant number of patients initially considered suitable for, and allocated to a Phase I trial, subsequently fail to enter the trial because of a deterioration in performance status which might have been avoided had the interval between first visit and treatment commencement been shorter. Our data indicate that this is actually an uncommon event (only four cases); nevertheless, it is important that this interval is kept as short as possible in the interests of good patient care.

In the era of increasingly challenging targeted therapies, the need for clinical expertise in new drug evaluation is clearly mounting.[10] In particular, significant efforts should be made to increase the recruitment rate in early clinical trials so that new promising agents can be tested as quickly as possible and also so that more patients can be offered the opportunity of benefiting from experimental treatments.

Conflict of interest statement

None declared.

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