EUROPEAN JOURNAL OF CANCER 46 (2010) 2739–2745

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

A study of the pattern of hospital admissions in a specialist Phase I oncology trials unit: Unplanned admissions as an early indicator of patient attrition ☆

Andre T. Brunetto [1], *Joo Ern Ang* [1], *David Olmos, Daniel Tan, Jorge Barriuso, Hendrik-Tobias Arkenau, Timothy A. Yap, L. Rhoda Molife, Udai Banerji, Johann de Bono, Ian Judson, Stan Kaye* *

Drug Development Unit, The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, Sutton, United Kingdom

ARTICLE INFO

Article history:
Received 16 April 2010
Received in revised form 22 June 2010
Accepted 22 June 2010
Available online 11 August 2010

Keywords:
Oncology Phase I trial
Unplanned admission
Hospitalisation
Risk stratification

ABSTRACT

Background: Unplanned hospital admissions (UHAs) in the context of oncology Phase I trials are important, yet rarely reported.

Methods: All patients admitted to the Royal Marsden Hospital Phase I clinical trials unit during February and March of 2005–2007 were included. The patient-, admission- and trial-related variables were collected. Correlations were sought between the occurrence of UHAs and the baseline patient/trial-related characteristics.

Results: Of the 308 admissions involving 177 patients, UHAs constituted 21% of all the admissions and 38% of the total bed occupancy. The majority of UHAs were cancer related (78%) and their occurrence was associated with a significant early patient attrition. Using multivariate analysis, the factors significantly associated with UHAs included age >60 years (RR 2.32, confidence interval (CI)-95% 1.12–4.81), ⩾3 metastatic sites (RR 3.26, CI-95% 1.54–6.90) and LDH > ULN (RR 2.18, CI-95% 1.06–4.46), with albumin <35 g/dL trending to significance ($p = 0.052$). The trials that contained cytotoxic chemotherapy incurred disproportionately higher rates of admissions (69.5%) than the trials that did not.

Conclusions: UHAs constitute a substantial workload and impact on the speed and cost of, as well as resource allocation in Phase I oncology trials. The majority of UHAs are cancer rather than treatment related. The risk stratification to guide patient selection may help reduce the incidence of UHAs.

© 2010 Elsevier Ltd. All rights reserved.

1. Introduction

Cancer is a leading cause of death worldwide. Of concern, the number of global cancer deaths is projected to increase by 45% (from 7.9 million to 11.5 million deaths) from 2007 to 2030.[1] Over the past decades, despite significant advances in our understanding of the molecular basis of cancer and the approval of a number of molecularly targeted agents, the clinical drug development process remains slow, costly and inefficient with a high attrition rate at the Phase III stage.[2]

☆ Presented in part at the: (1) 45th Annual Meeting of the American Society of Clinical Oncology, 2009, Orlando, Florida, USA. (2) Joint 15th Congress of the European Cancer Organisation and 34th Congress of the European Society for Medical Oncology, Berlin, Germany.

* *Corresponding author:* Address: Drug Development Unit, The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, Downs Road, SM2 5PT Sutton, United Kingdom. Tel.: +44 (0) 208 6426011; fax: +44 (0) 208 6427979.
E-mail address: Stan.Kaye@icr.ac.uk (S. Kaye).

[1] These authors contributed equally.

0959-8049/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2010.06.123

Phase I clinical trials are a critical first step in the process of anti-cancer clinical drug development and are generally carried out in patients with solid tumours resistant to standard anti-cancer therapies. They are usually small, non-randomised dose-escalation studies with the primary aim of defining the recommended Phase II dose of a novel agent (monotherapy or in combination with other agents or treatment modalities). Overall, the aims of the Phase I trials are to assess novel compounds in the shortest period of time, with minimal risks to patients.[3]

The conduct of Phase I trials of investigational novel agents represents unique challenges to oncologists and drug developers alike.[3–7] For the oncology team, the logistical challenges in the conduct of Phase I trials are no less important than the medical and nursing ones. These specialised physicians and nurses need to provide optimal, holistic care for patients, yet the administration of these interventions necessarily occurs within a fluid, dynamic environment with limited resources, including time, bed-space and staff. Unfortunately, there is a paucity of reports pertaining to the hospital admissions in this context, and thus little past experience to draw from the existing medical literature.

We were keen to examine the patterns of, reasons for and predictors of unplanned hospital admissions in the setting of a dedicated Phase I oncology clinical trials unit. Our previous experience indicates that unplanned admissions add an additional level of complexity in the conduct of these studies. For example, these admissions inevitably use up limited bed space with the potential to displace patients who are admitted for protocol-driven indications. Despite this, there is a strong preference for Phase I clinical trial patients to be managed within the specialist Phase I unit (and not elsewhere) to enable the prompt and accurate identification, reporting, causality assessment and treatment of any emergent problems, especially serious adverse events.

Elucidating information regarding unplanned hospital admissions serves to highlight the trends and the areas for improvement, by identifying common causes and specific groups of patients at high risk of unplanned admissions. In particular, this benchmarked experience may provide a reference and guide resource planning in other units. To our knowledge, this is the first published analysis which aims to identify the pattern and characteristics of unplanned hospital admissions in a dedicated Phase I clinical trials unit within a comprehensive cancer centre.

2. Patients and methods

2.1. Study design and patients

Included in this analysis were all patients with advanced cancers, refractory to standard therapies, who were admitted under the care of the Phase I clinical trials unit at the Royal Marsden NHS Foundation Trust (Sutton, United Kingdom) during three time intervals: from (1) 1st February 2005 to 31st March 2005, (2) 1st February 2006 to 31st March 2006 and (3) 1st February 2007 to 31st March 2007. All patients included in this analysis provided signed informed consent and met the eligibility criteria for the Phase I trial for which they were enrolled. The primary objective for this study was a description of the pattern of hospital admission in a specialist Phase I oncology trials unit within a comprehensive cancer treatment centre, with a breakdown of the underlying reasons (patients and trials related factors), and an estimation of the rates of unplanned admissions as well as the early attrition rates from clinical trials due to unplanned admissions. The secondary objectives included correlation of the baseline clinical and demographic factors with unplanned (non-protocol required) admissions. This study was approved by the local institutional review board.

The data were obtained from the Royal Marsden Hospital (RMH) patient records and Drug Development Unit Trial Log. The demographic and laboratory variables of patients at the trial enrollment were recorded and included age, sex, tumour type and histology, performance status (PS), albumin, LDH, number of metastatic sites and the distance from the patient address to the RMH (using the shortest distance estimated using a standardised online route planner). The recorded trial-related factors for each patient included dates of enrollment, administration of their first and last doses and the end of the study date. The reasons for and dates of each admission were recorded. The unplanned admissions were classed as treatment-related when it was caused by an adverse event evaluated as possibly, probably or definitely treatment-related. The total number of active trials, active patients and new patients enrolled was also collected. All the hospital admissions were classified as planned (i.e. dictated by protocol) or unplanned (the latter includes prolongation of hospitalisation beyond the trial-related purposes for any reason, and requiring at least one additional overnight stay).

2.2. Statistical analysis

The risks (or cumulative incidence) for unplanned admission and early attrition from Phase I clinical trials related to unplanned admission were calculated as follows: (1) number of patients with unplanned admissions divided by the total number of active patients and (2) number of patients dropping out of Phase I trials for non-treatment related reasons prior to becoming evaluable for safety and tolerability by trial definition divided by the number of new patients enrolled. The associations between the baseline characteristics of patients at study entry and the type of admission (planned or unplanned) were explored using the Chi-square, Fishers' exact, Mann–Whitney *U* and Spearman rank tests as appropriate. A logistic regression model was applied to define the baseline characteristics associated with the unplanned admissions in the multivariate analysis. All the *p*-values presented were two-sided and 95% confidence interval (CI) was estimated for all rates and relative risks. The SPSS programme (Version 15.0. Chicago, United States of America) was used for statistical analysis.

3. Results

3.1. Phase I trial activity

Fig. 1 illustrates the Royal Marsden Phase I unit activity from February 2005 to March 2007, with an outline of the trial activities and admissions pattern for each studied time interval.

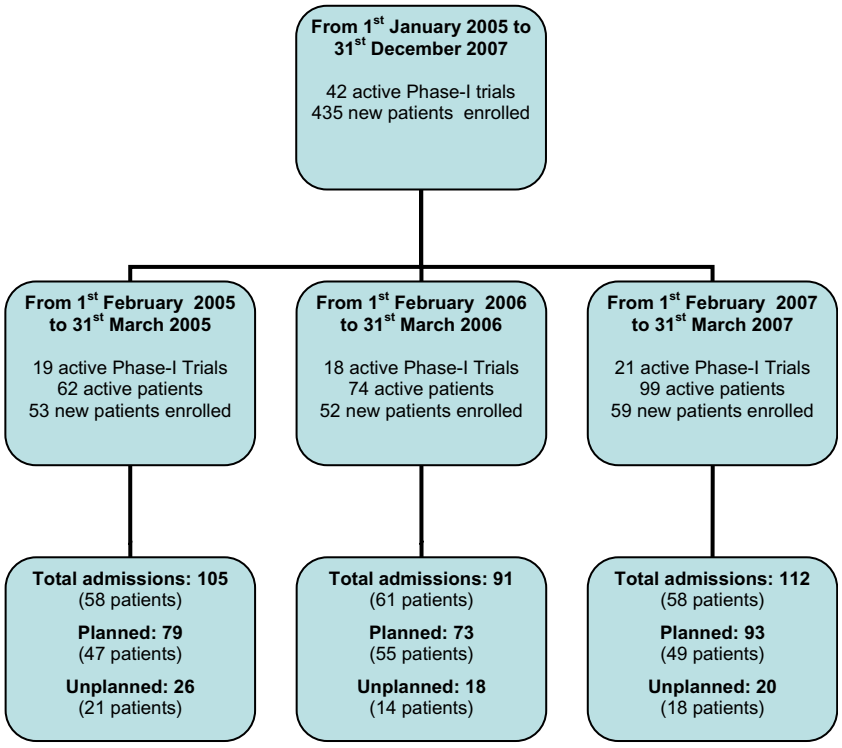

Fig. 1 – Study flowchart.

There were a total of 42 active trials over three years (i.e. January 2005–December 2007) which enrolled 435 patients. In February–March of 2005, 2006 and 2007, the number of active Phase I trials (with overlap) was 19, 18 and 21, respectively. The total numbers of active (and newly enrolled) patients for each time interval were 62 (53) for 2005, 74 (52) for 2006 and 99 (59) for 2007. It was on this background that the examined hospital admissions took place.

3.2. *Admissions characteristics*

A total of 308 admissions were identified for the study periods. This amounted to an inpatient occupancy of 680 bed-days with a median duration of 1 d (range 1–20). Of these, 64 admissions (20.8%) were unplanned and the remaining 244 were required according to the respective trial protocols. The unplanned admissions contributed to 257 bed-days and represented 37.8% of the overall bed occupancy in our unit during these periods. The median durations of planned and unplanned admissions were 1 (range 1–7) and 2 d (range 1–20), respectively.

Table 1 outlines the reasons for hospital admissions. Briefly, planned admissions were for the administration of treatment, monitoring of safety and sampling for pharmacokinetic and pharmacodynamic studies. In all, 78% of unplanned admissions were for the treatment of disease-related complications and symptom control, and 22% were for the management of treatment-related toxicities.

Two-hundred and fourteen admissions (69.5% of all the admissions) occurred in patients who took part in the cytotoxic chemotherapy-containing trials; of these, 167 were planned, while 47 of these were unplanned but the difference between the proportions of patients in chemotherapy-containing trials between the planned and unplanned cohorts was insignificant. The median distances travelled by patients per hospital admission were 37.3 miles (range 1.1–376) and 58.1 miles (range 1.1–245) for planned and unplanned admissions, respectively, but this difference was not statistically significant ($p = 0.13$).

Table 1 – Reasons for planned and unplanned admissions.

Reason for hospital admission in Phase I trials	N	%
Planned admissions	244	
Treatment and monitoring (including pharmacokinetic sampling)	225	92.2
Central venous device insertion	10	4.1
Research tumour biopsies (only)	7	2.9
Imaging studies (only)	1	0.4
Screening assessments requiring admission	1	0.4
Unplanned admissions	64	
Transfusion of blood products	12	18.8
Sepsis	11	17.2
Pain control	11	17.2
Constitutional	6	9.4
Palliative procedure	5	7.8
Neurological emergency	5	7.8
Intestinal obstruction	4	6.2
Metabolic	2	3.1
Thromboembolism	2	3.1
Disease-related dyspnoea	2	3.1
Death	2	3.1
Pathological fracture	1	1.6
Inflammatory pneumonitis	1	1.6

3.3. *Patient characteristics*

One-hundred and seventy seven patients of the 235 active patients enrolled in the Phase I studies were admitted at least once during the 6 months analysed. Fig. 1 illustrates the distribution of patients in the three different time intervals. The median age at study enrollment was 59.1 (range 18.7–81.7) and the male/female ratio was 2.3. One-hundred and nineteen (67.2%) patients were treated in trials with molecularly targeting agents only and 45 (25.4%) in trials with combinations involving at least one conventional cytotoxic agent. The most common tumour types were genitourinary tract tumours and sarcomas with 39 patients in each group (22%), and lung carcinomas and mesothelioma with 24 patients (13.6%). The distribution of all tumour types and other baseline patients characteristics is summarised in Table 2.

One-hundred and fifty one patients enrolled in 34 different studies required a protocol-driven admission. For each patient, the median number of planned admissions was 1 (range 1–6) and the median number of total days admitted due to protocol driven causes was 2 (range 1–16). Fifty three patients of a total of 235 active patients enrolled in Phase I studies required at least one unplanned admission in our series, with a median number of 1 (range 1–2) and median duration of 3 d (range 1–20). The estimated risk of having an unplanned admission was 22.6% (CI-95% 17.2–27.9). From these 53 patients, seven were admitted during or after screening and never started the experimental treatment; and 36 discontinued study after an unplanned admission. Four of the latter 36 did not complete the dose-limiting toxicity (DLT) evaluation period due to causes other than drug related toxicity. Therefore, for a patient newly enrolled in a Phase I trial, the

Table 2 – Baseline patient characteristics.

Characteristic	Total (n = 177)		Planned (n = 124)		Unplanned (n = 53)		p-Value
Age							
Median (range)	59.1 years (18.7–82.7)		58.7 years (18.7–82.7)		62.7 years (25.1–82.6)		0.027
Sex							
Male	124	70.10%	57	46.00%	17	32.10%	0.086
Female	53	29.90%	67	54.00%	36	67.90%	
Tumour type							
Sarcoma	39	22.00%	27	21.80%	12	22.60%	0.949
Genitourinary	39	22.00%	27	21.80%	12	22.60%	
Lung and mesothelioma	24	13.60%	17	13.70%	7	13.20%	
Gynaecological	19	10.70%	14	11.20%	5	9.40%	
Melanoma	19	10.70%	12	9.70%	7	13.20%	
Gastrointestinal	17	9.60%	13	10.50%	4	7.50%	
Breast	7	4.00%	6	4.80%	1	1.90%	
Others	13	7.30%	8	6.50%	5	9.40%	
Treatment							
Molecularly targeted	119	67.20%	86	69.40%	33	62.30%	0.140
Chemotherapy based	45	25.40%	27	21.80%	18	34.00%	
Hormones-endocrine	7	4.00%	7	5.60%	0	0.00%	
Virus therapy	6	3.40%	4	3.20%	2	3.80%	
Performance status							
ECOG 0	55	31.10%	45	36.30%	10	18.90%	0.005
ECOG 1	105	59.30%	71	57.30%	34	64.10%	
ECOG 2	17	9.60%	8	6.40%	9	17.00%	
Serum LDH							
Normal ($\leqslant$1 * ULN)	97	54.80%	77	62.10%	20	37.70%	0.003
High (>1 * ULN)	80	45.20%	47	37.90%	33	62.30%	
Serum albumin							
Low albumin (<35 g/dL)	95	53.70%	59	47.60%	36	67.90%	0.013
Normal albumin ($\geqslant$35 g/dL)	82	46.30%	65	52.40%	17	32.10%	
Number of organs involved							
$\leqslant$2 organs	90	50.80%	74	59.70%	16	30.20%	0.0003
$\geqslant$3 organs	87	49.20%	50	40.30%	37	69.80%	
Distance from home to RMH							
Median (range)	38.6 miles (1.1–376)		29.2 miles (1.1–376)		46.2 miles (3.3–245)		0.183

LDH = lactate dehydrogenase, ULN = upper limit of normality. RMH: Royal Marsden Hospital. The category of number of organs involved at baseline was defined as previously.[11]

estimated risk of early attrition related to an unplanned admission was 6.7% (CI-95% 2.9–10.5%).

3.4. Trials characteristics

The patients who were admitted within the study periods were enrolled in 36 different clinical trials. Of note, 20 were first-in-human trials and 12 were Phase Ib studies combining novel agents with cytotoxic chemotherapy, another molecularly targeted agent or radiotherapy. The routes of administration of the investigational novel agent included intravenous (i.v.) (20 trials), oral (13), i.v. and oral (2) and intra-tumoural (1). The ranges of mechanistic and molecular targets of these agents were wide, and the characteristics of these clinical trials are summarised in Table 3.

3.5. Predictors of unplanned admissions

The univariate analysis of nine different baseline patient characteristics (Table 2) showed that greater age, worse PS, an elevated serum LDH, a low serum albumin (<35 g/dL) and ⩾3 organs involved by metastatic disease were significantly more common in patients having an unplanned hospital admission. Patients who had unplanned admissions were more frequently males but this difference did not reach statistical significance ($p = 0.086$). The prevalence of the different tumour types was not significantly different between the planned and unplanned groups of patients. Multivariate analysis of the five significant factors derived from the univariate analysis detected the following independent baseline predictors associated with the patients having unplanned admissions (Table 4): ⩾3 organs involved by metastatic disease (relative risk (RR) 3.26, CI-95% 1.54–6.90), age >60 years (RR 2.32, CI-95% 1.12–4.81) and serum LDH > ULN (RR 2.18, CI-95% 1.06–4.46). Serum albumin <35 g/dL also showed a trend to statistical significance (p-value = 0.052, RR 2.04, CI-95% 0.99–4.20).

Table 3 – Trial characteristics.

Characteristics of trial	N	%
Type of Phase I		
First time in human	20	56
Novel molecularly targeted drugs	17	47
Novel cytotoxic	2	5
Viral therapy	1	3
Single agent pharmacodynamic studies	2	5
Single agent pharmacokinetic studies	1	3
Phase Ib disease specific studies	1	3
Phase Ib combinations studies	12	33
Chemotherapy-based combinations	9	25
Molecularly targeted drugs combinations	2	5
Novel agents with radiotherapy	1	3
Drug administration		
Intravenous	20	56
Oral	13	36
Oral and intravenous	2	5
Intra-tumoural	1	3
Target of Phase I trial		
Antiangiogenic	10	28
Antimitotic/apoptosis	4	11
EGFR/HER2	4	11
HDAC	4	11
Novel cytotoxic	4	11
DNA repair and methylation	3	8
HSP-90	2	6
IGF-1R	2	6
Reovirus	2	6
CYP17,20-lyase/17α-hydroxylase	1	3
Chemotherapy-based combinations		
Taxane	5	56
Platinum salt	3	33
Anthracycline	1	11

Epidermal growth factor receptor (EGFR); human epidermal growth factor 2 (HER2); histone deacetylases (HDAC); heat-shock protein (HSP); insulin growth factor (IGF).

4. Discussion

This study sought to examine the trends in, reasons for and predictors of unplanned hospital admissions in a specialist Phase I clinical trials unit within a comprehensive cancer centre. The results suggest that a significant proportion (37.8% in this study) of bed occupancy in the Phase I trials unit is being taken up by the unplanned hospital admissions, with consequent implications for the workload of staff in the unit, as well as the global cost and speed of novel anti-cancer drug development.

Overall, the unplanned hospital admission rate due to treatment-related complications was low at 22% which reflects an acceptable tolerability of these regimens. The finding that the early drug development process in cancer patients is generally safe is concordant with previous reports in the literature.[8–12] Moreover, the factors examined in the study revealed that the patient and disease-related variables, specifically age >60 years, ⩾3 metastatic sites and serum LDH > ULN, constituted the strongest independent predictors of Phase I trial participants incurring unplanned admissions. A risk-stratification strategy to guide patient selection in order to mitigate the risk of patient attrition and harm in Phase I trials has been widely investigated in various Phase I trial units throughout the world and our data add to the strength of this approach.[11–15]

Two of the parameters (⩾3 metastatic sites and serum LDH > ULN) identified in this study are common to published prognostic factors in Phase I, with a third (serum albumin <35 g/dl) trending to significance[11–13,15]; this is not unexpected as one would expect those patients with the baseline characteristics portending a worse prognosis to be more

Table 4 – Risk factors for unplanned admissions.

Characteristic	p-Value	Relative risk	CI-95%
⩾3 involved MTS sites/organs	0.002	3.26	1.54–6.90
Age >60 years	0.024	2.32	1.12–4.81
Serum LDH > 1 * UNL	0.034	2.18	1.06–4.46
Serum albumin <35 g/dL	0.052	2.04	0.99–4.20
Performance status ECOG 2	0.149	2.22	0.75–6.53

vulnerable to complications related to malignancy or therapy, thereby resulting in unplanned hospital admissions. Age (>60 years) has not been described previously but could well be attributed to patient fragility, reduced physiological reserves, medical comorbidities and a lower threshold of attending physicians towards the admission of more elderly patients.

Another observation was that of the significant attrition rates of those patients who incurred an unplanned admission. Such patients often discontinued the clinical trial participation prior to completing the treatment during the DLT-defining time window (usually days 1–28 of study). These patients would also need to be replaced for a formal evaluation of safety and toxicity. Hence, the cost of conducting the clinical trial is inadvertently escalated with incurred delays in dose-escalation decision making.

Cytotoxic chemotherapy-containing trials resulted in a disproportionately higher rate of admissions. Eleven trials with 45 patients required a total of 214 admissions, which represented 69.5% of all the admissions in our study. There was no significant difference between the rates of planned and unplanned admissions related with chemotherapy-based trials. Overall, these data indicate that chemotherapy-containing trials demand more inpatient space and care due to trial-related and trial-independent reasons.

There are clear limitations to this hypothesis-generating, retrospective, single-centre study. The number of cases and time intervals sampled are limited but the decision was made to study inpatient admissions in 2-month periods over three years as it was deemed to be a reasonable approach in capturing representative cases and patients receiving treatment in the unit. February and March were chosen, as this represents a time of the year when the Phase I unit is typically busy with minimal interruptions by public holidays. Also, three consecutive years were studied to allow cases from a larger overall window of time to be obtained. In addition, we had access only to the unplanned admissions that occurred in our unit (and not elsewhere); this could have introduced bias in our analyses. The patients living further away from our hospital might be expected to have a lower likelihood of being admitted to our unit. However, this did not demonstrate a significant association between patients with at least one unplanned admission and those who had none. Interestingly, there was even a trend showing that the unplanned cohort lived further away compared to the controls.

Overall, these data and our collective experience support the conduct of Phase I studies of anti-cancer agents by trained health personnel in dedicated units with the appropriate infrastructure. This allows the efficient assessment of novel therapeutic agents, whilst maximising chances of clinical benefit and optimising care of participating patients who have very complex needs.

5. Conclusions

In summary, an estimated 21% of all the admissions and 38% of the total bed occupancy in this dedicated RMH Phase I unit are non-trial protocol driven; these constitute a substantial burden to patients, and lead to increased workload, costs and time required to complete these already costly and risky ventures. Unplanned admissions related to therapy-related complications were infrequent (approximately 22%); more commonly, they occurred to facilitate palliation of cancer-related symptoms. These non-protocol driven admissions were also associated with a significant rate of early patient attrition. In this study, multivariate analysis revealed the baseline factors significantly associated with the unplanned admissions; these confirm previously reported prognostic factors and provide further validation of this risk stratification approach in optimising patient selection in Phase I clinical trials. A large, multi-centre European study aimed at providing further insight into these issues is now underway.

Conflict of interest statement

The authors do not have any relevant conflicts of interest to declare.

Acknowledgements

The Drug Development Unit of the Royal Marsden NHS Foundation Trust and The Institute of Cancer Research are supported in part by a programme grant from Cancer Research U.K. Support was also provided by the Experimental Cancer Medicine Centre (to The Institute of Cancer Research) and the National Institute for Health Research Biomedical Research Centre (jointly to the Royal Marsden NHS Foundation Trust and The Institute of Cancer Research).

REFERENCES

1. Boyle P, Levin B. *World cancer report*. World Health Organisation International Agency for Research on Cancer; 2008.
2. Tan DSW, Thomas GV, Garrett M, et al. Biomarker-driven early clinical trials in oncology – a paradigm shift in drug development. *Cancer J* 2009;**15**(5):406–20.
3. Verweij J. 'No risk, no fun': challenges for the oncology phase I clinical trial time-performance. *Eur J Cancer* 2008;**44**(17):2600–7.
4. Markmann M. The ethical dilemma of phase 1 clinical trials. *CA Cancer J Clin* 1986;**36**:367–9.
5. Daugherty C, Ratain MJ, Grochowski E, et al. Perceptions of cancer patients and their physicians involved in phase I trials. *J Clin Oncol* 1995;**13**:1062–72.
6. Cheng JD, Hitt J, Koczwara B, et al. Impact of quality of life on patient expectations regarding phase I clinical trials. *J Clin Oncol* 2000;**18**(2):421–8.
7. Nurgat ZA, Craig W, Campbell NC, Bisset JD. Patient motivations surrounding participation in phase 1 and phase 2 clinical trials of cancer chemotherapy. *Br J Cancer* 2005;**92**:1001–5.
8. Decoster G, Stein G, Holdener EE. Responses and toxic deaths in phase I clinical trials. *Ann Oncol* 1990;**1**:175–81.
9. Roberts TG, Goulart BH, Squitieri L, et al. Trends in the risks and benefits to patients with cancer participating in phase 1 clinical trials. *JAMA* 2004;**292**:2130–40.

10. Horstmann E, McCabe MS, Grochow L, et al. Risks and benefits of phase 1 oncology trials, 1991 through 2002. *N Eng J Med* 2005;**352**(9):895–904.
11. Arkenau HT, Olmos D, Ang JE, et al. Clinical outcome and prognostic factors for patients treated within the context of a phase I study: the Royal Marsden Hospital experience. *Br J Cancer* 2008;**98**:1029–33.
12. Arkenau HT, Barriuso J, Olmos D, et al. Prospective validation of a prognostic score to improve patient selection for oncology phase I trials. *J Clin Oncol* 2009;**27**:2692–6.
13. Arkenau HT, Olmos D, Ang JE, et al. 90-Days mortality rate within the context of a phase I trial: how should we identify patients who should not go on trial? *Eur J Cancer* 2008;**44**(11):1536–40.
14. Eisenhauer EA, O'Dwyer PJ, Christian M, Humphrey JS. Phase I clinical trial design in cancer drug development. *J Clin Oncol* 2000;**18**:684–92.
15. Penel N, Vanseymortier M, Bonneterre M, et al. Prognostic factors among cancer patients with good performance status screened for phase I trials. *Invest New Drugs* 2008;**26**(1):53–8.