Defining the risk of toxicity in phase I oncology trials of novel molecularly targeted agents: a single centre experience


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Background: This study defined the risk of serious toxicity in phase I trials of molecularly targeted agents (MTA).

Patients and methods: A retrospective analysis of toxicity data from patients treated in phase I trials of MTAs was carried out to define the rate of treatment-related grade 3/4 toxic effects, deaths and risk factors associated with grade 3 or more toxicity.

Results: Data from 687 patients [median age, 59.1 years (range 12.5–85.5)] treated in 36 trials were analysed. Two hundred and eleven patients were of Eastern Cooperative Oncology Group performance status (PS) zero, 432 of PS one, 38 of PS two and 6 unknown. The rate of grade 3 and 4 events was 14.1% (n = 97) and 1.9% (n = 13), respectively. Twenty-four percent of events were gastrointestinal, 22% constitutional and 20% metabolic. PS two was associated with a higher risk of toxicity [odds ratio (OR), 2.6; 95% confidence interval (CI) 1.1–6.1; P = 0.032] as was receiving >100% of maximum tolerated dose or maximum administered dose (OR 2.5; CI 1.8–3.9; P < 0.001). Mortality rate was 0.43% (n = 3).

Conclusions: Therapy with novel MTAs in phase I trials is associated with a moderate risk of significant toxicity. This appears less than in phase I studies involving cytotoxic agents, particularly in relation to grade 4 toxicity. The risk of death is low.

Key words: molecularly targeted therapy, phase I, risk, toxicity

Introduction

Despite recent advances in therapies for advanced cancers, the majority of patients die as a result of metastases from their disease. However, a higher proportion of patients are surviving longer, in many cases maintaining a good performance status (PS) and therefore becoming candidates for phase I trials.

Phase I trials are designed to define and evaluate a maximum tolerated dose (MTD), optimum schedule and toxicity of new agents. Patients participating in these trials face many uncertainties, including the benefit/risk ratio. Several studies over the past 20 years have quantified the benefit of participating in phase I trials: response rates have been reported as between 4% and 10% with a median overall survival of 6 months [1–8]. With the development of the novel molecularly targeted agents (MTA), a clinical benefit rate of 20%–25%, to include patients with meaningful stable disease with those with objective tumour response, has been reported [4, 8]. Some of these studies have identified prognostic indicators for clinical benefit, which may aid in patient selection for phase I trials [4, 5, 8, 9, 10], including our own Royal Marsden Hospital (RMH) score [8].

Risk is usually defined as the rate of significant—usually National Cancer Institute—Common Toxicity Criteria (NCI-CTC) grade 3 or more toxic events and toxicity-related death. The risk of treatment-related death associated with participation in phase I trials has been reported as being 0.5% [1, 4–8]. Fewer studies have reported on the risk of grade 3 or more toxicity; three studies have reported a rate of 10%–36% for ≥3 grade toxicity [5, 6] and 14% for grade 4 events [7].

The development of toxicity is implicit in the overall conduct of phase I trials, and it will be significant in a defined number of cases. However, the experience of a significant toxic event in a patient with a poor prognosis has clinical and quality-of-life implications. Clinicians treating patients in phase I trials should be able to define the risk associated with experimental treatments to assist patients in undertaking the decision to undergo such therapies as patients often underestimate the impact of significant treatment-related toxicity associated with phase I agents. In addition to quantifying risk, identifying factors predictive for serious...
toxicity may further aid patient selection for such trials. Finally, as the majority of the aforementioned referenced studies were carried out over long periods of time with a focus on classical cytotoxic agents, we feel it is necessary to assess these parameters in the era of MTAs, which are now more relevant to cancer therapy.

This retrospective study reviewed clinical data from patients treated in phase I trials of MTAs, with the aim of defining: (i) the rates of grade 3 or more treatment-related toxic effects, (ii) the nature of these toxic effects, (iii) the treatment-related death rate and (iv) factors associated with onset of grade 3 or more treatment-related toxicity.

patients and methods

patient characteristics

We reviewed the demographic and clinical data of consecutive patients treated on phase I trials of MTAs between January 2005 and December 2009. These patients were selected from a database of 1143 patients treated on all trials (n = 73) within the Drug Development Unit at the RMH/Institute of Cancer Research during the study period. Patients treated in phase II trials, non-dose escalating phase I trials and phase I trials involving classical cytotoxic agents and oncolytic viral agents were excluded (Figure 1).

This study was approved by the Royal Marsden Clinical Research and Development Committee. All phase I trials included in the analysis were approved by a Research Ethics Committee. Inclusion and exclusion criteria across all studies were similar. As per standard phase I trial design, patients were evaluated at least weekly via history, physical examination and laboratory assessments reducing in some protocols to a minimum interval of 4 weekly after two to four cycles. Any events occurring between scheduled visits were also reported. Patient clinical notes, case report forms and serious adverse event (AE) forms were reviewed to obtain the following data: patient demographics and cancer history, clinical and laboratory data and Eastern Cooperative Oncology Group (ECOG) PS at study entry, occurrence of grade 3 or more at least possibly treatment-related toxicity, nature, treatment and outcome of toxic event and occurrence of treatment-related death. Toxicity was defined using the NCI–CTC-AE, version 3.0. Classification of toxic effects was as follows: cardiovascular, constitutional, dermatological, gastrointestinal (GI), haematological, infection, metabolic, neurological, ocular and respiratory. All deaths reported as possibly, probably or definitely related to treatment, and confirmed as such with the sponsor, were captured.

An MTA was defined as any agent with an extra- or intracellular target different from those associated with conventional chemotherapy (DNA, tubulin or cell division machinery; novel cytotoxic agents were included). Trials were grouped into one of seven categories according to the target of the agent under investigation: cell cycle and apoptosis, DNA repair and chromatin remodelling, cytoplasmic signalling proteins, growth factor receptors, protein folding and degradation and ‘others’.

statistical methods

Descriptive statistics were used to describe patient, trial and toxicity characteristics. Toxicity and death rates were calculated as the:

\[ \text{number of patients with at least one event} \div \text{total number of patients} \times 100 \]

Toxicity rates and total number of events per year were compared using a chi-square test. A prognostic association between baseline clinical and laboratory characteristics and the appearance of a grade 3 or more treatment-related toxicity were analysed using a chi-square test, Fisher’s exact test, Spearman’s rank correlation coefficient or Mann–Whitney U test when appropriate. All variables with a P value of ≤ 0.2 in the univariate analysis were introduced in a logistic regression model for the multivariate analysis. In the multivariate analysis, all variables with a P value of ≤ 0.05 were considered significant. Data analysis was carried out using SPSS 17.0 (Chicago, IL).

results

patient characteristics

A total of 687 patients treated in 36 trials of MTAs were included. The median age was 59.1 years (range 12.5–85.5 years) and 49.2% (n = 338) of patients were female. Thirty-one percent (n = 211) of patients were of ECOG zero, 63% (n = 432) ECOG one and 6% (n = 38) ECOG two. Patients had received a median of 2 (range, 0–13) previous lines of treatments. The most common tumour types were GI (23.3%), gynaecological (15.7%) and sarcoma (11.6%). Other baseline characteristics are summarised in Table 1.

trials

Of the 36 phase I trials included in this analysis, 9 were of agents targeting DNA repair and chromatin remodelling (n = 178; 26%), 7 were of agents targeting angiogenesis (n = 98; 14%), 5 were of agents targeting cytoplasmic signalling proteins (n = 122; 18%) and growth factor receptors (n = 159; 23%) (each), 4 were of agents targeting cell cycle and apoptosis (n = 53; 8%) and protein folding and degradation (n = 29; 4%) (each) and 2 agents had miscellaneous targets (c17, 20 lyase and aminopeptidase; n = 48; 7%).

Toxic effects

We reported a total of 165 grade 3 and 4 events in 110 patients during the study period (Table 2). The overall risk of grade 3 toxicity was 14.1% and of grade 4, 1.9%. Sixty-seven patients (9.8%) experienced grade 3 or more toxic effects during the first cycle of treatment, but only in eight cases were these events classified as dose-limiting toxic effects as per the
An additional 27 patients (3.9%) experienced grade 3 or more toxic effects during the second cycle of treatment, and another 16 patients (2.3%) experienced grade 3 or more toxic effects beyond cycle 2. There was no significant difference in the year-on-year rate of grade 3 or more toxicity (12.4%–19.2%) between 2005 and 2009 ($P = 0.436$).

The most common types of toxic effects reported were GI (24%), constitutional (22%) and metabolic (20%; Figure 2).
Nausea, vomiting and diarrhoea accounted for 65% of GI toxic effects, transaminitis accounted for 41% of metabolic events and fatigue was the key constitutional toxicity. There were a total of three deaths during the study period assessed as at least possibly related to drug. Thus, the treatment-related mortality rate was 0.43% with no significant differences on the year-on-year rate as shown in Table 3.

**Factors predicting for toxicity**

Twenty-two variables were analysed in the logistic regression analysis of prognostic factors for toxicity (Table 4). In the univariate analysis, receiving >100% of MTD or maximum administered dose (MAD; \( P < 0.001 \)), PS two versus zero to one (\( P = 0.014 \)), elevated bilirubin (\( P = 0.023 \)) and the presence of liver metastases (\( P = 0.014 \)) were associated with an increased risk of toxicity. However, in the multivariate analysis, the significant prognostic factor predictive for grade \( \geq 3 \) toxicity was \([\text{odds ratio (OR)}; 95\% \text{ confidence interval (CI)}]\) receiving >100% of MTD or MAD (OR 2.5; 95% CI: 1.6–3.9; \( P < 0.001 \)) and PS two versus zero to one (OR 2.6; 95% CI: 1.1–6.1; \( P = 0.032 \)).

**Discussion**

The recent acceleration of the development and approval of MTAs mandates a re-analysis of the risk of toxicity and mortality associated with these agents in the phase I setting. Our study has several advantages over previous similar studies in that we evaluated actual patient data, (as opposed to published data of completed trials [6]), collected over a short

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**Figure 2.** Classification of grade 3 and 4 at least possibly drug-related toxic effects.

**Table 3.** Toxicity and mortality rate

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 687)</th>
<th>2005 (n = 96)</th>
<th>2006 (n = 105)</th>
<th>2007 (n = 156)</th>
<th>2008 (n = 160)</th>
<th>2009 (n = 170)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3</td>
<td>97</td>
<td>14.1</td>
<td>16</td>
<td>13</td>
<td>12.4</td>
<td>24</td>
</tr>
<tr>
<td>Grade 4</td>
<td>13</td>
<td>1.9</td>
<td>2</td>
<td>2.1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>110</td>
<td>16</td>
<td>18</td>
<td>16.4</td>
<td>13</td>
<td>11.8</td>
</tr>
<tr>
<td>Mortality</td>
<td>3</td>
<td>0.43</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 4.** Uni- and multivariate factors predicting for toxicity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate, ( P )</th>
<th>Multivariate, ( P )</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose: percentage of MTD/MAD received</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>2.5 (1.6–3.9)</td>
</tr>
<tr>
<td>PS 2 versus 0–1</td>
<td>0.014</td>
<td>0.032</td>
<td>2.6 (1.1–6.1)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>0.023</td>
<td>0.143</td>
<td>1.0 (0.9–1.1)</td>
</tr>
<tr>
<td>Liver metastases</td>
<td>0.014</td>
<td>0.2</td>
<td>1.3 (0.9–2.0)</td>
</tr>
<tr>
<td>Age</td>
<td>0.074</td>
<td>0.120</td>
<td>1.1 (0.9–1.1)</td>
</tr>
</tbody>
</table>

Variables entered into univariate and multivariate analysis: dose as percentage of MTD or MAD (0–33%, 34–66%, 67–100% or >100%); tumour type; age, gender; ECOG PS; haemoglobin; total white blood cell count; lymphocyte count; platelet count; albumin; lactate dehydrogenase; alanine aminotransferase; aspartate aminotransferase; alkaline phosphatase; bilirubin; number of sites of metastatic disease; presence of liver metastases, lung metastases and bone metastases; number of lines of previous systemic treatments; comorbidities: concurrent liver disease, immunosuppressive/autoimmune disease, gastrointestinal disease, diabetes, cardiovascular disease or pulmonary disease. All variables were those present at study entry. CI, confidence interval; MAD, maximum administered dose; MTD, maximum tolerated dose; OR, odds ratio; PS, performance status.
period of time (4 years, as opposed to up to 12 years [1, 5, 6]) giving a picture of the current status of oncology drug development.

The results of this analysis of 687 patients treated in phase I trials of MTAs over a 4-year period demonstrated a 16% risk of grade 3 or more toxicity, the majority occurring during the first and the second cycles of drug administration. In addition, this risk has remained constant over time. We have previously reported a 3% rate of grade 3 or more toxic effects associated with MTAs, with 50% of these occurring after the first cycle. However, this was in relation to specific GI, skin and clinical renal toxic effects [11]. Other retrospective studies of phase I trials largely based around cytotoxic agents have shown that phase I trials are associated with a risk of 10%–30% of grade 3–4 toxic effects [5, 6]. Several factors may be cited for this difference—the improvement in supportive care and the change in toxicity grading systems over the 10-year time period are examples of these. In addition, as grade 4 haematological toxicity is frequently observed with cytotoxic chemotherapy and though usually clinically not relevant, such events would be reported in clinical trials and lead to a high rate of grade 4 reported events. The most frequent types of toxic effects that we report included GI, metabolic and constitutional; this is typical of MTAs, with less haematological and cardiovascular toxicity. Differing patient populations in this and previous studies could be a contributing factor; though on inspection of the patient profiles, patient characteristics were broadly similar. However, the most recent report on the area of toxic effects in phase I trials showed that the rate of grade 4 events with targeted therapies was in the order of 5%–13%, suggesting that there may be a real difference in the rate of significant AEs when compared with cytotoxic-based phase I trials [7].

Knowledge of factors that predict for toxicity can aid in patient selection for phase I trials. Our analysis identified that an ECOG PS of two and receiving >100% of MTD or MAD was predictive for the onset of grade 3 or more toxicity. The importance of these factors can be explained by the fact that (i) a patient with a PS of two is less likely to have sufficient reserve to withstand toxic drug effects and (ii) in general, toxicity increases with increasing dose. Of note, no previous analyses of toxic effects in phase I trials have demonstrated either of these factors as being of significance. Hence, these factors may relate uniquely to trials of MTAs. Bachelot et al. [5] showed that age >65 years was associated with a higher risk of toxicity, alongside dose level at entry. In contrast, Han et al. [4] showed that toxicity was associated with the use of cytotoxic agents, high platelet counts, female gender and low white blood cell (WBC) count. The difference between these studies and ours could be related to the patient population and the types of agents tested; for example, an elevated platelet count in a cancer patient is associated with a poor prognosis. Similarly, patients with a lower WBC are likely to be immunocompromised and may have received extensive prior myelosuppressive therapy, leading to a higher risk of toxicity with classical cytotoxic agents. Interestingly, neither of the parameters of our RMH risk score for survival in phase I trials (low albumin, more than two metastatic sites and elevated lactate dehydrogenase) nor the RMH score itself were predictive for toxicity, suggesting that the parameters governing survival in phase I trials are different from those that govern risk of developing significant toxicity. Finally, we acknowledge that the results of this study are based on a retrospective analysis and a prospective validation of the findings will be undertaken.

We demonstrated a mortality rate of 0.43% which is in line with that of ~0.5% reported in other analyses of mortality in phase I oncology programmes [1, 5–7] as well as a previous analysis of patients participating in all phase I trials in our unit [8]. Furthermore, our data suggest that the risk of death has remained constant. This, alongside the increase in the reported response rates from 5% in older studies to ~10% in more recent studies [8], suggests that the benefit-risk ratio for patients may be improving over time. This in turn may be reflective of the increased experience with use of these agents by phase I oncologists [6].

In conclusion, we demonstrate that the risk of developing serious toxicity associated with phase I trials of MTAs is relatively low. Factors at study entry that predict for a higher risk of toxicity include a low PS score and receiving a dose of >100% MTD/MAD. The development of significant toxicity is integral to the end point of phase I trials and is key to the definition of MTD and dose-limiting toxicity; it is therefore essential that those patients exhibiting this toxicity are representative of the general population of cancer patients. It is also important to limit the number of patients with significant toxicity in phase I trials to those who will be most informative towards the study goals. Judicious patient selection is therefore essential, at all stages (dose escalation/expansion) of phase I trials.

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disclosure

The authors declare no conflicts of interest.

references

Clinical biopsychosocial risk factors for depression in lung cancer patients: a comprehensive analysis using data from the Lung Cancer Database Project


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Background: Various risk factors for depression in lung cancer patients have been suggested but have been examined separately in studies with relatively small sample sizes. The present study examined the biopsychosocial risk factors of depression in lung cancer patients, focusing on psychological factors in the largest patient sample reported to date.

Patients and methods: A total of 1334 consecutively recruited lung cancer patients were selected, and data on cancer-related variables, personal characteristics, health behaviors, physical symptoms, and psychological factors were obtained. The participants were divided into groups with or without depression using the Hospital Anxiety and Depression Scale.

Results: Among the recruited patients, 165 (12.4 %) manifested depression. The results of a binary logistic regression analysis were significant (overall $R^2$, 36.5 %), and a greater risk for depression was strongly associated with psychological factors, such as personality characteristics (neuroticism) and coping style (low fighting spirit, helplessness/hopelessness, and anxious preoccupation). Although the contributions of cancer-related variables, personal characteristics, health behaviors, and clinical state were relatively low, cancer stage, cancer type, sex, and age correlated significantly with depression.

Conclusion: Depression was most strongly linked with personality traits and coping style, and using screening instruments to identify these factors may be useful for preventive interventions.

Key words: coping, depression, lung carcinoma, personality, quality of life, supportive care