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Original Research

A study of 1088 consecutive cases of electrolyte abnormalities in oncology phase I trials

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Abstract ***Background:*** The incidence and clinical significance of electrolyte abnormalities (EAs) in phase I clinical trials are unknown. The objective of this study is to evaluate the incidence and severity of EAs, graded according to CTCAE, v4.03, to identify variables associated with EAs and their prognostic significance in a phase I population.

Methods: A retrospective chart review was performed of 1088 cases in 82 phase I clinical trials consecutively treated from 2011 to 2015 at the Drug Development Unit of the Royal Marsden Hospital. Cox regression analysis was performed to examine the relationship between overall survival (OS) and baseline characteristics, treating the occurrence of grade III/IV EAs as a time-varying covariate.

Results: The most common emergent EAs (all grades) were as follows: hyponatraemia 62%, hypokalaemia 40%, hypophosphataemia 32%, hypomagnesaemia 17% and hypocalcaemia 12%. Grade III/IV EAs occurred in 19% of cases. Grade III/IV EAs occurred during the dose-limiting toxicity window in 8.46% of cases. Diarrhoea was associated with hypomagnesaemia at all grades ($p < 0.001$), hyponatraemia at all grades ($p = 0.006$) and with G3/G4 hypokalaemia ($p = 0.02$). Baseline hypoalbuminaemia and hyponatraemia were associated with a higher risk of developing other EAs during the trial in the univariate analysis. Patients who developed grade III/IV EAs during follow-up had an inferior median OS (26 weeks vs 37 weeks, hazard ratio = 1.61; $p < 0.001$).

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Conclusion: This is the first study to demonstrate the clinical significance of baseline hypoalbuminaemia and hyponatraemia, which are predictors of development of other EAs in phase I patients. Grade III/IV EAs are adverse prognostic factors of OS independent of serum albumin levels.

1. Introduction

The development of molecularly target agents for cancer has resulted in novel adverse events (AEs) correlating with the mechanism of action of these agents. AEs due to anti-cancer treatment are a common form of iatrogenic injury and as molecularly targeted therapies are generally administered continuously, cumulative toxicities can occur [1,2]. Some AEs caused by this class of drugs are preventable, but many are unanticipated and differ with those of other therapeutics such as conventional cytotoxic agents and immunotherapies. The incidence of metabolic toxicities in phase I studies is not well documented, particularly with regards to electrolyte abnormalities (EAs) and their consequences. These toxicities can range from asymptomatic laboratory findings to symptomatic alterations that can worsen patients' quality of life and lead to death.

The treatment for EAs may range from oral supplementation to anti-cancer therapy interruption and intravenous supplementation, which increases the costs and risks of drug development. Although they appear easier to treat compared with other observable toxicities, the clinical significance of EAs in phase I trials is unknown. In many clinical trials, asymptomatic laboratory toxicities are excluded from dose-limiting toxicity (DLT) assessment as their real clinical significance is doubted. Nevertheless, these toxicities have significant implications on resources, including medical assessment time, laboratory tests, hospital admissions and pharmacy time.

The prognostic significance of some EAs is well described for several tumour types, such as hypercalcaemia for breast and kidney cancer and hyponatraemia for small cell lung cancer [3,4]. However, the incidence, prevalence and the clinical significance of EAs in oncological phase I studies are not well documented, and the reasons for developing these AEs are poorly understood.

Establishing the prevalence of the electrolyte alterations can help to recognise, prevent and optimally manage them. Furthermore, attempting to understand the risk factors associated with EAs can help refine inclusion/exclusion criteria. To the best of our knowledge, there is no study exploring the overall risk of EAs in the phase I cancer setting. We aimed to study the prevalence of EAs of patients on oncology phase I studies, elucidate potential risk factors and assess their relevance and impact in the drug development process of new agents.

2. Materials and methods

The principal objective of this study was to determine the incidence and severity of EAs in a cohort of phase I cancer patients. Secondary objectives were to evaluate the association of EAs with other clinical features and laboratory tests and to estimate the prognostic significance of EAs in the phase I setting. Approval to collect and analyse the data was obtained by applying to the committee for clinical research at The Royal Marsden NHS Foundation Trust as a service evaluation (SE541).

A retrospective chart review was performed of 1088 patient cases with solid tumours in 82 phase I clinical trials consecutively treated from 01/01/2011 to 31/12/2015 in the Drug Development Unit of The Royal Marsden, who were diagnosed with any type of electrolyte disturbance. All data were anonymised before analysis. The clinical and demographics details including age, sex, comorbidities, date of last follow-up and date of death were collected. To be included in this study, patients must have received at least one dose of the experimental drug. The phase I trials included dose escalation and expansion of different classes of drugs, such as protein kinase B (AKT), poly ADP ribose polymerase (PARP), ataxia-telangiectasia and Rad3-related (ATR), Mammalian Target of Rapamycin (mTOR), phosphoinositide-3 kinase (PI3K) and anti-folate receptor inhibitors, used as single agents and/or in combination.

For this project, hypokalaemia, hyperkalaemia, hypocalcaemia, hypercalcaemia, hypomagnesaemia, hypermagnesaemia, hypophosphataemia, hyponatraemia and hypernatraemia were defined and graded according to the Common Terminology Criteria of Adverse Events (CTCAE), version 4.03 [5].

Overall survival (OS) was calculated from date of first treatment to date of death and censored at date of last follow-up. Cox regression was used to examine the relationship between OS and baseline characteristics, treating the occurrence of grade III/IV EAs as a time-varying covariate. Grade III/IV EAs during the first 4 weeks of the trial were analysed using a logistic regression model. Backward stepwise regression with a p-value of 0.2 was used to select variables for a multivariate logistic regression analysis. Impact of different variables such as age, sex, comorbidities and death were analysed. Chi-square and Fisher's exact test were used to evaluate the univariate and multivariate analyses along with 95%