

Clinical outcomes and survival of patients with hematological malignancies enrolled into Phase I clinical trials

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Abstract

Phase I clinical trials are primarily designed to assess the safety and toxicity of a new agent and determine the recommended dose for further trials that assess efficacy. Patients entering these trials typically have multiply relapsed or refractory disease and would otherwise receive supportive treatment. The collective outcomes of patients enrolled onto phase I trials in solid tumors but not in hematological malignancies have previously been reported. We analyzed the overall outcomes and survival of 91 patients enrolled onto one of 14 Phase I and I/II trials for hematological malignancies at a dedicated early phase trials unit within a tertiary hematology unit. Median time on trial was 3.7 months (range 0-24), 32% experienced grade 3 or 4 adverse events. The overall response rate was 41%, overall survival 18 months (95% confidence intervals 5-30 months) and progression free survival 7 months (95% CI 1-13), although there was a significant difference according to underlying hematological cancer subtype. Response rate was strongly associated with survival time. On multivariate analysis, disease subtype and LDH at time of trial entry showed an association with survival rate. These results demonstrate that the outcomes of patients with hematological malignancies entering phase I trials is better than expected.

Introduction

Advances in the understanding of the biology of hematological malignancies and innovative technologies have resulted in a number of novel therapies entering into phase 1 clinical trials. Whilst individual studies are reported according to protocol defined endpoints, an overall view of the outcomes of patients with hematological malignancies has not been described. In solid cancers this has been previously published and a prognostic score at trial entry proposed.¹⁻³

The primary objective of phase 1 trials is to assess the safety and tolerability of investigational agents and to determine the recommended phase 2 dose. They are not generally statistically powered to assess efficacy which is typically determined in later phase trials.^{4,5} Whilst patients generally enter early phase trials in the hope of deriving clinical benefit, published data of response rates are often quoted around 5% with a treatment related mortality of 0.5% (although more recent publications have demonstrated an improvement in response to approximately 10% in solid tumors).^{1,2,6} The response rate is often used as a preliminary indicator of efficacy, which in competitive drug development may take significant weighting when companies decide to move to phase 2. However, there may be a discordance between response and survival outcomes in molecularly targeted or immunotherapeutic approaches.⁷ Patients entering phase 1 studies are usually those that have no standard treatment options available, but still retain a good performance status and organ function to meet the strict trial eligibility criteria. Once these patients leave the trial treatment due to disease progression or toxicity, their options are generally limited to supportive care or to potentially enter another trial. This information is not generally collected in Phase 1 trials which would be limited to progression free and sometimes (but not always) overall survival.

The purpose of this analysis was to investigate the overall outcomes of patients with hematological malignancies treated in phase 1 trials. Data were collected from a dedicated early phase trials unit within a large UK hematology tertiary centre. The primary objectives were to assess overall response rate (ORR), overall survival (OS) and progression free survival (PFS). The secondary objectives were to assess adverse events and whether patients had further treatment following the end of study. Exploratory objectives were to identify potential predictive markers of outcome.

Methods

Patients

All patients with a histologically proven hematological malignancy enrolled onto a Phase I or Phase I/II trial between March 2012 and February 2017 that had taken at least one dose of the study drug were included in this retrospective analysis. Data was collected from patient electronic medical records. Toxicity was assessed and graded according to the National Cancer Institute- Common Toxicity Criteria version 4.03, causality of the adverse events was determined by the investigators. All study patients had provided written informed consent for participation in the relevant trial, which were all approved by the UK Health Research Authority.

Clinical outcomes and statistical analysis

Data cut-off for all patients was 31st March 2017. Responses were defined as per trial protocols, based on international working group criteria for each disease group.⁸⁻¹² OS was calculated from the start of therapy on trial to death and PFS defined from the start of

therapy to death or confirmed disease progression. Both were censored at time of last follow-up or at the time of autologous stem cell transplant (ASCT).

Descriptive statistics were used to characterise demographic and clinical parameters. *P* values were calculated using Kruskal Wallis for non-parametric data, and χ^2 for comparing proportions. Median follow-up time was calculated using the reverse Kaplan-Meier method. OS and PFS were analysed with the Kaplan-Meier method and the log rank test was used to assess the differences in median survival between different patient groups. Cox proportional hazard regression model was used to perform multivariable analysis. All statistical tests were 2-sided and $P < 0.05$ was considered statistically significant.

Statistical analyses were performed using Prism Version 5.0 (Graphpad software, La Jolla, California) and IBM SPSS Statistics for Windows Version 24.0 (Armonk, NY).

Results

Trials overview

There were 14 trials (Phase I and Phase I/II) that recruited patients between 2012 and 2017, six for myeloma, five for lymphomas and three for leukemias and myelofibrosis. The investigational agents were monoclonal antibody (three trials) and a small molecule inhibitor (11 trials), of which five were in combination with another agent. Four of the trials were first-in-human studies.

Patient characteristics

Overall, 84 patients were recruited to at least one of the trials, seven were enrolled onto two trials and each entry was considered a separate event. Baseline characteristics of patients are summarised in Table 1. For analysis, patients were grouped according to disease subtype. Fourteen patients had leukemia/ myelofibrosis (MF) (12 acute myeloid leukemia, AML; 2 MF), 28 patients had lymphoma (DLBCL, $n=14$; follicular lymphoma, $n=2$; mantle cell lymphoma, $n=6$; marginal zone lymphoma, $n=1$; lymphoplasmacytic lymphoma, $n=1$; Hodgkin's disease, $n=2$; ATLL, $n=1$; and T cell lymphoma, $n=1$) and 49 had myeloma. Median number of months from diagnosis to commencing trial was 56, 23 and 7 months for patients with myeloma, lymphoma and leukemia/ MF respectively.

Toxicity and time on trial

Adverse events attributable to the investigational agent were experienced by 85% of the patients and were predominantly grade 1-2. Thirty patients (33%) had at least one week's interruption of trial drugs as a result of the toxicities (Table 1).

Of the 91 patients, 80 had discontinued the trial at the data cut-off time point. This was for progressed disease in 50 cases and "lack of efficacy" (investigator decision due to stable disease) in 4 further cases. Twelve patients came off trial due to toxicity, eight mandated by the trial protocol (including 5 dose limiting toxicities, DLT), and four due to patient decision. Three patients completed the set number of treatments on protocol (16 cycles in one case and 6 in the other two), ten were taken off trial to proceed to ASCT and one came off study following a revision of the histological diagnosis (Figure 1). No toxicity related deaths occurred.

The median time on trial treatment was 3.67 months (range 0-24) with a median of 4 cycles (range 0-27). There was a significant difference ($P < 0.001$) in the length of time on trial by disease subtype, patients with myeloma had a median of 5 months on trial compared to 2 months for lymphoma and 3 months for leukemia/myelofibrosis (Table 1). Fifty patients

(63%) went on to received further treatment either on (20%) or off trial (80%), the remaining patients received supportive care only.

Response rates and survival

Nine patients came off trial prior to first formal response assessment, five for progressive disease based on the clinical picture, one patient with a DLT, two due to patient decision and one due to revision of the histological diagnosis. Best response was assessed in the remaining 82 patients. Overall response rate for the 82 response-evaluable patients was 45%, and 41% in the whole cohort. Two patients achieved a complete response, CR, 35 a partial response, PR (including 14/40 patients with myeloma achieving a very good partial response, VGPR). There was a significant difference in ORR according to underlying disease with 60% of myeloma patients responding compared to 29% for lymphoma and 18% for those with leukemia/ myelofibrosis, $P < 0.001$ (Figure 2). Sub-group analysis of responses by age demonstrated an ORR of 46% for < 65 years old and 33% in ≥ 65 years ($P = 0.2$), however this varied considerably according to disease groups, as younger patients with myeloma did significantly better than older, but the converse was true for patients with lymphoma (Supplementary Table 1). The majority of patients that entered into the trials were young, with just seven patients over 75 years (4 with lymphoma, 2 AML and 1 myeloma), only one of whom achieved a PR.

After a median follow-up of 20 months (95% CI 11-29 months) the median OS was 18 months (95% CI 5-30 months) with a 2 year OS of 44%. Median PFS was 7 months (95% CI 1-13) with a 2 year PFS of 18% (Figure 3a and b). Again, there was a significant difference in survival rates according to disease subtype: patients with myeloma had a median OS of 37 months compared to 6 months for lymphoma and 4 months for leukemia/ myelofibrosis ($P < 0.001$) (Supplementary Table 2, Figure 3c and d). The median survival of the 50 patients that went on to receive further treatment was 7 months following the end of the Phase 1 trial (range 0-39 months).

Exploratory analyses were performed to investigate if patient related factors such as age and disease related factors, such as number of prior lines of therapies, and potential prognostic markers correlated with survival (summarised in Supplementary Figure 1 and Figure 4). In univariate analysis, hemoglobin of $\geq 100\text{g/L}$ showed a trend toward superior OS, median OS: 24 months versus 7 months, ($P = 0.07$). Raised LDH was significantly associated with worse survival, OS, 6 versus 33 months, ($P < 0.0001$) (Supplementary Figure 1). When patients were categorised as above and below 65 years (WHO definition of elderly), no difference in survival was observed between the two groups, however when the higher age cut-off of 75 years was taken, median survival was just 5.5 months compared to 24 months in the rest of the cohort, $P = 0.06$ (Figure 4). No other variables reached statistical significance.

Multivariable analysis was performed for hemoglobin $\geq 100\text{g/L}$, albumin $\geq 35\text{ IU/L}$, LDH $\leq 225\text{IU/L}$, age and disease type. However only LDH (HR 0.36, 95% CI 0.17-0.77, $P = 0.009$) and disease type (HR 2.0, 95% CI 1.3-3.2, $P = 0.001$) were significantly associated with outcome (Table 3).

Factors on trial, such as response rate, dose interruptions and toxicity were also analysed according to OS (Figure 5). Response rate was strongly correlated with outcome, both overall and within the disease subgroups. Responders (PR or better) had a median OS that was not reached compared to 8 months in those who did not achieve at least a partial response ($P < 0.0001$). Patients with G3 or 4 toxicity related to the trial agent did not have a significantly difference survival rate to those who did not have severe toxicities. Patients who had a dose interruption of greater than a week had a median survival of 25 months compared to 10 months, $P = 0.05$.

Discussion

Data from Phase 1 clinical trials are important for the rapid evaluation and development of novel agents for cancers. This is evidenced by agents gaining FDA and EMEA breakthrough designation on the basis of phase 1 data, for example GSK2857916 for the treatment of relapsed and refractory myeloma.¹³ Additionally phase 1 trial designs have evolved from a simple “3+3” dose escalation to Bayesian type modelling to reduce the number of patients at sub-therapeutic doses and more accurately predict the correct phase 2 dose.^{14, 15} The American Society of Clinical Oncology (ASCO) recently revised their policy statement on the role of Phase I trials in cancer research and treatment, emphasising their therapeutic intent.¹⁶ Indeed, as with our cohort, ASCO commented that many patients enrolled onto these trials do go on to have further therapy. This challenges the paradigm that Phase I trials are offered to patients with no other options except for palliation.

This study aimed to assess the outcomes for patients with hematological malignancies enrolled onto early phase trials. The overall response rate of 41% for the whole cohort was better than expected for a population with relapsed or relapsed/ refractory disease. This may partly reflect the strict eligibility criteria common to early phase trials, skewing the population. This data compares very favourably to the overall responses seen in patients with solid malignancies of approximately 10%, representing the better outcomes often seen with myeloma and lymphoid malignancies.^{1-3, 6} Even within this dataset there was considerable variation in response depending on the underlying disease, as patients with myeloma were significantly more likely to achieve a PR or better than those with lymphoma (predominantly aggressive lymphomas), and particularly those with relapsed AML or myelofibrosis highlighting the natural history of these diseases. The poor survival for those with AML indicates that this continues to be an unmet need and that traditional Phase 1 trial design to investigate targeted compounds as single agents may not be an effective way to assess their efficacy or safety in this cohort of patients. The improved response rate in myeloma was reflected in the survival outcomes. The median OS of this cohort was 18 months, with a median PFS of 7 months, again favourable with regard to solid malignancies in which the OS ranges from 5-10 months.^{1, 3, 17-19} Significant survival differences according to disease were also observed.^{1, 2, 6} In this dataset, a correlation between response and survival was observed, hazard ratio 0.16 (95% CI 0.09-0.32, $P < 0.0001$).

Age was not found to be predictive of survival in the analysis at the cut-off of 65 years old. This is similar to comparable analyses in patients with solid tumours.²⁰⁻²² Whilst none of these trials had an upper age limit, clearly there was a bias in patient selection. This may reflect clinician assessment of frailty and suitability for experimental treatments and/ or that older patients were less willing to participate in phase 1 trials. Indeed, when a higher cut-off of 75 years was used, a difference in response and survival was apparent although the numbers of patients were small.

Similarly, number of previous lines of therapy, which may be considered a prognostic marker, was not associated with outcome, which may be due to the individual trials eligibility criteria.

Multiple studies have sought to identify prognostic markers for survival in patients treated in phase I trials, mainly in those with solid malignancies.^{18, 19, 23-28} The most established prediction model, the Royal Marsden score, uses three parameters of albumin $< 35\text{g/L}$, LDH $>$ upper limit of normal and > 2 sites of metastases. This score was derived from analysis of the survival of 212 patients treated at this single centre, and has since been validated by other groups.^{1, 3, 18} Whilst this score could not directly be applied to patients with

hematological malignancies, LDH was an independent prognostic variable in this cohort (hazard ratio: 0.36, 95% CI 0.17-0.78), although albumin was not.

Approximately one third of patients experienced grade 3 or 4 toxicity, however this did not associate with outcome. Perhaps paradoxically, those who experienced a dose interruption of greater than a week had an improved median survival compared to those who did not (25 months versus 10 months), this could be explained partly by the longer time on treatment enjoyed by patients whose disease did not progress early on in the trial, such patients were perhaps more likely to have treatment interruptions.

In conclusion, the survival of patients from this cohort of hematological malignancies was better than expected and not that of a palliative population, with the exception of AML where survival remained poor. The better outcomes for those with myeloma and lymphoid malignancies may in part be due to patient selection, but also a reflection of the new therapies under evaluation. Importantly, a significant number of patients were able to receive further treatment following completion of the phase 1 study, with a median survival of 7 months once off trial. In multivariate analysis, a normal LDH was associated with an improved survival across the cohort. Further prospective studies are warranted to validate this and further explore the factors that influence patient outcomes in Phase 1 studies.

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Tables

Table 1. Patient Characteristics at trial entry, length of time on trial and toxicities

Table 2. Hazard ratios to assess survival according to age of patient, disease subtype, Hemoglobin $\geq 100\text{g/L}$, albumin $\geq 35\text{g/L}$ and LDH $\leq 225\text{IU/L}$

Figures

Figure 1. Consort diagram demonstrating the reasons that patients came off trial.

Figure 2. Best response of patients who had at least one response assessment.

Figure 3. Survival rates, OS (a) and PFS (b) in whole cohort and OS (c) and PFS (d) split by disease subtype

Figure 4. Overall survival according to age, above and below a) 65 years and b) 75 years

Figure 5. Overall survival according to a) response, b) G3/4 AE related to IMP and c) dose interruption for more than one week.