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Original Research

Clinical outcomes of adolescents and young adults with advanced solid tumours participating in phase I trials

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Abstract ***Background:*** Adolescent and young adult (AYA) patients with advanced solid tumours are often considered for phase I clinical trials with novel agents. The outcome of AYAs in these trials have not been described before.
Aim: To study the outcome of AYA patients in phase I clinical trials.
Methods: Clinical trial data of AYAs (defined as aged 15–39 years at diagnosis) treated at the Drug Development Unit, Royal Marsden Hospital, between 2002 and 2016, were analysed.
Results: From a prospectively maintained database of 2631 patients treated in phase I trials, 219 AYA patients (8%) were identified. Major tumour types included gynaecological cancer (25%) and sarcoma (18%). Twenty-five (11%) had a known hereditary cancer syndrome (most commonly BRCA). Molecular characterisation of tumours (n = 45) identified mutations most commonly in *TP53* (33%), *PI3KCA* (18%) and *KRAS* (9%). Therapeutic targets of trials included DNA damage repair (16%), phosphoinositide 3-kinase (PI3K) (16%) and angiogenesis (16%). Grade 3/4 toxicities were experienced in 26% of patients. Of the 214 evaluable

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patients, objective response rate was 12%, with clinical benefit rate at 6 months of 22%. Median overall survival (OS) was 7.5 months (95% confidence interval: 6.3–9.5), and 2-year OS was 11%. Of patients with responses, 36% were matched to phase I trials based on germline or somatic genetic aberrations.

Conclusion: We describe the outcome of the largest cohort of AYA patients treated in phase I trials. A subgroup of these patients demonstrates benefit, with several durable responses beyond 2 years. A sizeable proportion of AYA patients have cancer syndromes, significant family history or somatic molecular aberrancies which may influence novel therapeutic treatment options.

1. Introduction

Cancer in the adolescent and young adult (AYA) population constitutes < 5% of all malignant diagnoses [1]. However, there are reports of increasing incidence of major cancers, such as colorectal cancer, that are occurring in the AYA age group of patients [2,3]. Over the past few years, dramatic improvements have been made in the survival of paediatric and adult oncology populations, while AYA populations had lesser benefit [4,5]. These improvements in survival have occurred through a combination of improved care coordination, drug development, enrolment into clinicals trials and rapid incorporation of novel therapeutic agents into front-line standard-of-care therapy [1]. Several factors have been attributed to the reduced benefit in survival of AYAs, but the diversity of patients, lack of available clinical trials and difficulty in enrolment in clinical trials have been highlighted previously [1,6]. In contrast to children, AYA cancer patients are also less likely to be treated in an academic medical centre [7]. Consensus on the definition of the AYA population differs across regions [1]. The lower limit of age for AYAs ranges from 13 to 18 years, while the upper limit ranges from 24 to 39 years. It is important to note that most definitions use age at diagnosis (as compared to age at review). Apart from medical needs, AYA cancer patients also have age-specific social, emotional and developmental care needs which are unique, and they often experience difficulties in being met adequately [8,9].

AYAs are underrepresented in clinical trials, with little published data regarding their outcomes. Enrolment into clinical trials by AYA is lower than children and older adults [10,11]. However, several AYA cancer patients are treated in adult trials using novel therapeutic agents. These trials are often considered in these young patients because of their tendency to have good organ reserve and ability to tolerate additional lines of therapy. To date, there are no published data on the outcomes of the AYA population in adult phase 1 clinical trials. Our study describes the experience of a large cohort of AYA patients, treated in a specialised phase 1 adult cancer unit.

2. Methods

All consecutive AYA patients treated within phase I clinical trials in the Drug Development Unit at The Royal Marsden National Health Service Foundation Trust, Sutton, United Kingdom from March 2002 to March 2016 were included. For this study, AYA patients were defined as aged 15–39 years at the time of initial cancer diagnosis. However, these patients eligible for phase I trial participation had to be ≥18 years at the time of consent into the clinical trial but could be older than 39 years when entering the phase 1 trial as long as their initial cancer diagnosis was within the described AYA age range. They had advanced solid tumours for which approved treatments were no longer available. Patients were discussed at weekly trial allocation meetings to identify suitable trials based on disease characteristics, tumour molecular characterisation results (if available) and trial slot availability. Patients who received at least one dose of an experimental agent and provided written informed consent for participation in phase I trials as approved by the local research ethics committee were included in this study.

The following parameters that were prospectively collected for each clinical trial were collated: patient characteristics, tumour characteristics, laboratory results. For each phase I trial, drug name, class of drug, mechanism of action, date of starting trial, best response, grade of toxicities and date of progression were collected.

Toxicity data were collected as originally recorded in the electronic medical records or the case report forms when required. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events. Tumour responses were confirmed by a radiologist using Response Evaluation Criteria in Solid Tumours (v1.1). Clinical benefit rate

(CBR) was calculated as the sum of complete response (CR), partial response (PR) and proportion of patients with stable disease (SD) at 6 months.

2.1. Molecular characterisation

From 2011 onwards, patients treated at the Drug Development Unit, Royal Marsden, were consented to undergo characterisation of key molecular drivers in the patients' archival tumour tissue. Various panels of targeted next-generation sequencing have been used through the years. From 2013 to the mid-2015, 48 genes were tested using the TruSeq panel and from the end of 2015 to currently, 113 genes were tested using the GeneRead DNA damage panel. Immunohistochemistry for ataxia-telangiectasia mutated kinase (ATM) was performed from 2015. Panels and other additional tests were also dependent on the types of trials and the biomarkers being selected for these trials during that period of time. The results of these tests, if available, were used to match the molecular aberration identified to a rationally selected experimental trial, if available. For the purpose of this study, only those with results from the 48- and 113-gene next-generation sequencing panel were considered.

3. Statistical methods

Descriptive statistics were used to summarise patient and tumour characteristics. Progression-free survival (PFS) was defined as the time elapsed from day 1 on an experimental phase I trial until radiological progression or disease-related death (whichever occurred first). If no evidence of progression was documented at the last follow-up, patients were censored at the time of the last radiological evaluation. Overall survival (OS) was defined as the time between the day of the first administration of the experimental therapy and either the date of death from any cause or the last follow-up (if death was not observed during the follow-up period, the patient was censored at the last follow-up). For patients included in more than one trial, data for PFS and OS from the first experimental therapy were used. Median OS and PFS, as well as their 95% confidence intervals (95% CIs) were determined using the Kaplan–Meier method. Data are presented as survival plots, and the log-rank test was used to compare survival curves by patient subgroups. Data were analysed using Stata, v15.0.

4. Results

4.1. Patient and tumour characteristics

Between March 2002 and March 2016, from a database of 2631 patients, 219 (8%) patients were identified to fulfil the definition of AYAs with a diagnosis of solid tumours and were treated on a phase I clinical trial with a novel antineoplastic agent. Median age at diagnosis was 33 years, and median age at the time of entering clinical trial was 36 years. Most common tumour groups included gynaecological (25%) and sarcoma (18%), with females constituting 63% of the population. Median time from occurrence of metastatic disease to entering a phase I trial was 21 months (interquartile range [IQR]: 11–25 months). Patients had a wide range of previous lines of treatment (median 2, 32% one line, 36% two lines and 26% three or more lines), reflective of the number of standard lines of therapy available for each tumour type, before referral to a phase I trial. Documentation of the presence or absence of a family history of cancer at the first consultation in the phase I unit was only performed in 62% of cases. Of these, 28% had no family history of cancer, 18% had a known hereditary syndrome and 54% had a positive family history of cancer. Further details of patient and tumour characteristics are described in Table 1.

4.2. Phase I study outcomes

In total, 219 patients participated in 277 phase I trials. Most patients participated in a single phase I trial (81%), while 15% participated in two (range 1–6 trials). Therapeutic targets in various trials included the DNA damage repair (DDR) pathway, phosphoinositide 3-kinase (PI3K) pathway, antiangiogenic pathway, insulin-

Table 1
Patient characteristics.

N = 219	N (%)
Age at diagnosis: median, years (range)	33 (15–39)
Primary tumour	
Gynaecological	54 (25%)
Sarcoma	39 (18%)
Gastrointestinal	35 (16%)
Breast	25 (11%)
Others	66 (30%)
Gender	
Male	80 (37%)
Female	139 (63%)
Previous lines of treatment	
0	13 (6%)
1	71 (32%)
2	79 (36%)
3–6	56 (26%)
Family history	
Known hereditary syndrome	25 (11%)
Family history of cancer	74 (34%)
No family history of cancer	38 (17%)
No family history documented	82 (37%)
Time from diagnosis to metastatic disease	
Mean (months)	18
Interquartile range (months)	0–24
Time from metastatic disease to the first phase 1 study	
Median (months)	21
Interquartile range (months)	11–25

Table 2
Therapeutic targets of phase I studies AYA patients were enrolled into.

Therapeutic targets	N (%)
DNA damage repair pathway	36 (16%)
PI3K pathway	35 (16%)
Antiangiogenic agents	34 (16%)
IGF pathway	27 (12%)
Epigenetic agents	25 (11%)
Others	62 (28%)

AYA, adolescent and young adult; IGF, insulin-like growth factor; P13K, phosphoinositide 3-kinase.

like growth factor (IGF) pathway and epigenetic agents. Table 2 describes the various classes of phase I trial drugs into which patients were enrolled into.

4.3. Toxicities of phase I trials

Experimental therapies were well tolerated with the majority of toxicities being grade 1 or grade 2. Grade 3 or 4 toxicities were experienced by 26% of the patients, with non-haematological grade 3 or 4 toxicities in 16% and haematological in 11%. The most common toxicities were fatigue (87%), gastrointestinal (67%) and haematological (34%). The majority of toxicities occurred within the first month of treatment (67%). Dose reductions due to toxicity were required in 8%, while a further 21% of patients with toxicity were able to continue dosing with dose delays. Treatment-related inpatient admissions occurred in 13% of patients, and 11% of patients required cessation of therapy due to toxicity. There were no treatment-related deaths. Agents targeting the DDR pathway had the most common toxicities of fatigue, nausea and anaemia, and for the PI3K pathway, the most common toxicities were of fatigue, nausea and diarrhoea. Table 3 summarises the various toxicities experienced by patients.

4.4. Efficacy

Only 2% (n = 5) patients were deemed non-evaluable for response. Objective response was achieved in 12% of the population, with 2% (n = 4) achieving a CR and 10% demonstrating a PR to therapy. Seventy-nine patients (36%) achieved SD as their best response, with a CBR at six months of 22%. Responses predominantly occurred in breast (n = 8) and gynaecological malignancies (n = 11) but also occurred in other tumour types such as sarcoma (n = 3), glioblastoma multiforme, lymphoma, melanoma and adrenocortical tumours (n = 1, each). These responses were from trials targeting a range of antitumoural pathways: DDR (n = 6), antiangiogenesis (n = 5) and IGF (n = 3). Median PFS was 2.2 months (95% CI: 1.9 to 2.7; Fig. 1), and median OS was 7.5 months (95% CI: 6.3 to 9.5; Fig. 2). A small subgroup of patients had a PFS of more than 1 year (n = 15, 7%) on a phase I trial. Of those patients who survived more than 36 months, there was no major difference in characteristics compared with those with lesser survival, except for number of previous lines of treatment (1 [IQR 1–3] versus 2 [IQR 0–3]; p = 0.04) and grade 3–4 toxicity (25 versus 50%, p = 0.03; Table 4).

Table 3
Toxicities experienced during phase I trial.

Toxicity	Any grade	Grade 3/4
Fatigue	190 (87%)	17 (8%)
Cutaneous	53 (24%)	3 (1%)
Nausea/vomiting	137 (63%)	7(3%)
Diarrhoea	64 (29%)	7 (3%)
Mucositis	30 (14%)	3 (1%)
Neurotoxicity	21 (10%)	1 (<1%)
Anaemia	60 (27%)	8 (4%)
Neutropenia	21 (10%)	12 (5%)
Febrile neutropenia	2 (1%)	1(<1%)
Thrombocytopenia	28 (13%)	7 (3%)
Hepatic	57 (26%)	4 (2%)
Pneumonitis	4 (2%)	2 (1%)

4.5. Germline and tumour molecular characterisation

Twenty-five patients in this cohort had a known cancer predisposition syndrome (11%), including *BRCA1/2*-associated hereditary breast or ovarian cancer (n = 18) type 1 neurofibromatosis (n = 3), familial adenomatous polyposis (n = 2), Von Hippel-Lindau syndrome (n = 1) and Cowden syndrome (n = 1). Of those patients with known germline defects, twenty (80%) were allocated to a trial that targeted the underlying genetic aberration. Thirteen of such individuals were *BRCA1/BRCA2* mutation carriers assigned to trials involving poly ADP ribose polymerase (PARP) inhibitors (Table 5). Nine individuals

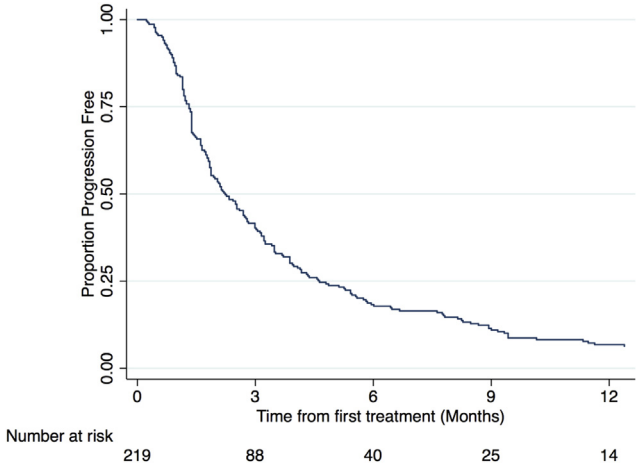

Fig. 1. Kaplan–Meier curve of PFS of AYA patients in phase I trials. Median PFS: 2.2 months (95% CI: 1.9 to 2.7). PFS, progression-free survival; AYAs, adolescents and young adults; CI, confidence interval.

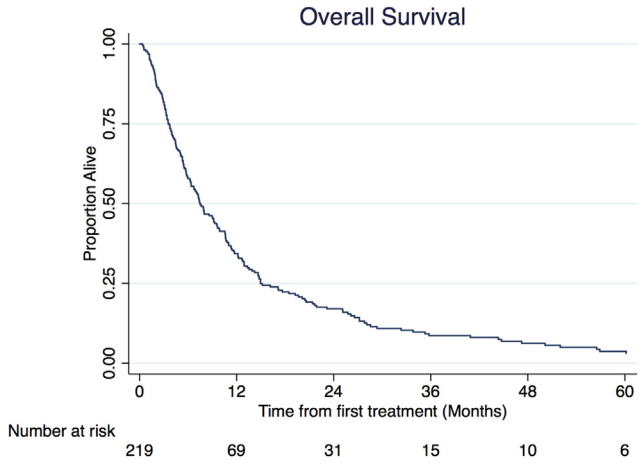

Fig. 2. Kaplan–Meier curve of OS of AYA patients in phase I trials. Median OS: 7.5 months (95% CI: 6.3 to 9.5). OS, overall survival; AYAs, adolescents and young adults; CI, confidence interval.

with known germline mutations also underwent tumour molecular profiling, but the results of this did not change their initial allocation. In total, tumour DNA from 45 individuals was analysed for somatic mutations using next-generation sequencing (48- or 113-gene panels). Recurrent variants of high predicted impact were identified in *KRAS, MET, TP53* and *PIK3CA*. Deleterious variants were identified in *BRCA1* and *BRCA2,* in patients already known to be germline BRCA mutation carriers. The frequency of reported variants was variable, ranging from 5 to 82%. A more detailed analysis of the germline and somatic mutations is reported by McVeigh *et al.* [12].

Table 4
Characteristics of long-term survivors.

Characteristic	Died or censored <36 months (n = 204)	Died or censored ≥ 36 months (n = 15)	P-value
Gender	N (%)	N (%)	
Female	128 (63%)	11 (73%)	0.58
Male	76 (37%)	4 (27%)	
Tumour type			
Gynaecological	47 (23%)	7 (47%)	0.10
Sarcoma	38 (19%)	4 (27%)	
Gastrointestinal	23 (11%)	0 (0%)	
Drug class			
Angiogenesis	29 (14%)	5 (33%)	0.56
DDR	34 (17%)	2 (13%)	
Epigenetic	24 (12%)	1 (7%)	
Grade 3/4 toxicity			
No	154 (75%)	7 (47%)	0.03
Yes	50 (25%)	8 (53%)	
	Median (IQR)	Median (IQR)	
Number of previous lines of treatment	2 (1–3)	1 (0–3)	0.04
Age (years)	33 (28–37)	28 (26–35)	0.08
Months from initial diagnosis to metastatic disease	8 (0–24)	11 (6–38)	0.14
Time from metastatic disease to phase I	17 (11–25)	19 (10–35)	0.60

DDR, DNA damage repair; IQR, interquartile range.

Table 5
Phase I allocation in patients undergoing tumour sequencing.

(n = 45)	N (%)
Targeting known gDNA mutation	9 (20)
Targeting somatic mutation	7 (16)
High mutation load identified (assigned to immunotherapy)	3 (7)
Targetable mutation but no slot on trial for targeted therapy	9 (20)
No targetable mutations identified	14 (31)
Allocated based on tumour type or immunophenotype	3 (7)

5. Discussion

Here we describe for the first time the largest cohort of AYA cancer patients that entered phase I clinical trials with prospectively collected data. The percentage of AYA patients in the total cohort of the Drug Development Unit was 8% which is in line with the total number of AYA patients aged 15–39 years described in epidemiological studies and as such is a representative cohort. Younger patients with advanced cancers are generally treated more aggressively by oncologists and undergo several lines of treatment, before being referred to a phase I unit. Owing to their good organ reserve, they often fulfil inclusion criteria to enter these trials. Whether referrals actually take place to phase I units often depends on the familiarity of the treating physician with experimental drug units. In contrast to paediatric patients who are treated centrally, patients aged between 18 and 39 years can be treated in many hospitals where referrals for experimental treatments are possibly not common. Interestingly, very little is known about the wishes and expectations of young adults who may be referred to phase 1 clinics.

One of the key end-points of phase I clinical trials is the determination of the maximum tolerable dose and recommended phase II dose. As such, systematic documentation of toxicities and adverse events on these trials are mandatory. Several studies have reported the occurrence of grade 3 or 4 toxicities in between 10 and 40% of patients [13–15], and in a study focussing on older individuals, grade 3 or 4 toxicities were reported to occur in approximately 25% of patients [16]. Our study shows a similar incidence of serious toxicities in phase I trials for the AYA population, suggesting that chronological age and fitness is less likely to play a role in the risk of suffering adverse events as is physiological fitness and performance status. Interestingly, the patients who survived longer than 36 months experienced more grade 3–4 toxicity, which maybe either due to the prolonged period on trial or due to a dose–effect relationship.

Precision medicine is transforming the management of most neoplastic conditions, where therapeutic decisions are guided by genomic or molecular features, rather than the primary site of origin. These features are often agnostic to age, and novel therapeutic agents are being developed to capitalise on the various vulnerabilities identified in these tumours. Unfortunately, most of these agents are currently still in clinical trial testing, and/or if approved, remain unaffordable to the majority of patients, and as such, access to these medications remains through enrolment in clinical trials. Within the AYA population, patients between the ages of 13 and 18 present a particular challenge. Most trials focussing on adult solid tumours would have a higher age cut-off, usually at the age of 18 years, which is the legal limit for independent consent in most countries. While paediatric trials may include AYA patients, their availability may be restricted to only high-volume academic medical centres and largely focused on paediatric malignancies [17,18]. The overall response rates and survival of AYA patients in phase I clinical trials in our study did not differ largely from other tumour groups or age group–specific studies [13–16]. However, it is important to highlight the small but sizable long-term survivor tail of approximately 5% of the cohort. For this group, with a median age of 30 years, long-term survival is probably even more meaningful as they may have young children, filial commitments and other age-specific reasons to feel indispensable.

It is important to note that molecular characterisation of somatic mutations in the tumours of the patients in this study cohort did not reveal a large number of specific mutations. The targeted panels used in our setting were not designed specifically for AYA patients, and as such, it is possible that oncogenic drivers of these tumours were not detected by these panels. The spectrum of tumour types that occur in the AYA population is distinct to those in the paediatric or older adult groups. Our study population displays this broad spectrum; however, it should be noted that this is also reflective of the local referral patterns and availability of trials in our unit and not particularly of the general AYA population in the United Knigdom. To the best of our knowledge, our study is the first to report the clinical outcomes of a large number of AYA patients who have participated in adult phase I clinical trials. We have demonstrated that AYA patients may benefit from treatment with novel therapeutic agents, with a small subgroup deriving considerable benefit and having long-term survival.

6. Conclusion

AYA patients aged 15–39 years at diagnosis of cancer may benefit from phase 1 clinical trials, with a few durable responses. Given the relatively good organ function, they may tolerate treatment relatively well. In this cohort, there were a considerable proportion with a family history of cancer or cancer syndromes, which are increasingly seen in AYA cancer patients and could influence the choice of novel treatment options.

Conflict of interest statement

None declared.

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