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SHORT REPORT

Increasing complexity in oncology phase I clinical trials

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Summary

Clinical trials in oncology have become increasingly complex because of incorporation of predictive biomarkers and patient selection based on molecular profiling of tumors. We have examined the change in procedures and work intensity in phase 1 oncology trials over the years with several parameters used as surrogates of complexity. Categories that were included as events were clinical evaluations, pharmacokinetic (PK) laboratory tests, non-PK laboratory tests, specific molecular or histological characteristics, questionnaires and subjective assessments, routine clinical and physical examinations, imaging, invasive procedures and others. The information was extracted using a standardized form including study type, tumor type, information on agent, participant characteristics and study mandated events during the first 3 cycles of each protocol. A total of 102 phase I oncology and hematology study protocols that were active at a single institution in 1996, 2006 and 2016 were evaluated. In 2016, there were significantly more ($P < 0.05$) median number of procedures, outpatient tests, subjective assessments, PK's, molecular profiling, biopsies and medication dispensing times. There were higher median numbers of procedures in studies in hematologic malignancies, testing immunotherapies and those with over 15 inclusion or exclusion criteria. These values also differed significantly ($P < .005$) when the median values were compared in nonparametric tests. Our results suggest that study related procedures in cancer phase I trials have substantially increased over the last two decades. The successful conduct of early-phase oncology clinical trials in future will require additional research resources.

Keywords Trials · Complexity · Phase I

Introduction

The drug development in oncology is experiencing a significant growth as the treatment paradigm of many cancers is rapidly changing. Some of the novel agents that have recently been approved by regulatory authorities include targeted therapies, immunotherapies, antibody-drug conjugates and chimeric antigen T cell receptors (CARs). As indicated by several recent Food and Drug Administration (FDA) breakthrough designations and conditional approvals based on phase I and II data, drug development process in oncology should be rapid, efficient and able to implement modern drug development models for upcoming novel drugs. An efficient and successful phase I research program can be challenging in light of an increased protocol complexity, restrictive inclusion and exclusion criteria, high personnel workload, stringent regulatory criteria and a restrictive budget to manage the work.

Contemporary therapies in cancer phase I trials are subject to newer endpoints with an effort to demonstrate a response signal or at least evidence of target inhibition [1, 2]. In fact, when ≥3% of patients show a partial response in a phase I trial, it's more likely that the drug being tested will eventually receive FDA approval [3]. Hence, the American Society of Clinical Oncology, emphasizes the need of an adequate trial design in the drug development process [4]. The clinical trial protocol design, especially in later phase trials, is one of the many factors that drive high and rising costs of drug development. In all clinical areas of development, the typical later-stage protocol has an average of 7 objectives and 13 endpoints of which at least half are supplementary. Furthermore, for phase III protocols, only 23.6% of all procedures support a regulatory compliance requirement [5]. Phase I protocols are known to be the most complex and burdensome to conduct with a mean of 30 procedures. Medical oncology has remained one of the top therapeutic areas consistently conducting more complex clinical trials [6].

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A complex phase I trial can ultimately impact timelines, cost and burden on patients and researchers. Data on the complexity of carrying out phase I cancer clinical trial remain limited [7] and most of the literature addressing clinical trial workload include all phases of clinical drug development [8, 9]. Depending on the study design, its complexity can be measured by the number of activities, people involved, disease, target population, study drug and other factors which all influence the complexity. The purpose of the current study is to analyze a series of phase I cancer clinical trials that were active in 1996, 2006 and 2016 at the Institute for Drug Development (IDD) to further examine and compare complexity over these years.

Methods

We evaluated a total of 102 phase I trial protocols that were active at our institution in 1996, 2006 and 2016. The information related to study, tumor type, agent, participant characteristics and study mandated events during the first 3 cycles of each protocol was extracted using a standardized form. For each year, procedures were defined as each study mandated event and procedure specified in the schedule of events; procedures were multiplied by their frequency to represent study complexity. Categories included as events were clinical evaluations, pharmacokinetic (PK) laboratory tests, non-PK laboratory tests, specific molecular or histological characteristics, questionnaires and subjective assessments, routine clinical and physical examinations, imaging procedures and others. Summary statistics were used to report the number of observations, median, mean and standard deviation. Nonparametric methods of comparison and Poisson regression analysis were implemented. All statistical analyses were two-sided. *P* value <0.05 was considered significant. Statistical analysis were performed in R 3.1.1 [10].

Results

There were 21 active trials in 1996, 32 in 2006 and 49 in 2016. Most of the studies were industry sponsored and of solid tumors. The total number of procedures (Table 1) were significantly higher in 2016 compared with 2006 and 1996 ($P < .001$).

In 2016, 90% of the studies were testing immune or targeted therapies. The mean number of pharmacokinetic (PK) time points and non-PK tests per protocol doubled from 1996 to 2016. Most of the studies in 2016 had over 15 inclusion and exclusion criteria defined in the study protocol. Other specific tests such as ECGs, functional imaging and molecular profiling were also higher in 2016 compared to 1996. CT scans/X-rays and clinic visits remained unchanged. Study medication dispensing also increased with a mean number of 15 dosing times in 2016 compared to six in 1996 (Table 1). Furthermore, the mean number of outpatient tests, procedures and subjective assessments had increased with time. All the above parameters differed significantly when median values were compared using non-parametric tests.

We also looked at how certain trial elements influenced the number of procedures in these protocols. For instance, there was higher median number of procedures seen in studies for hematologic malignancies, those testing immunotherapies and trials with over 15 inclusion or exclusion criteria (Fig. 2). There was also significantly higher median number of procedures in those studies with longer consent form. Although the number of procedures was higher in those protocols with over 100 pages, they did not correlate with the number of protocol amendments or study type (Figs. 1 and 2).

Discussion

Phase 1 trials have become more complex with substantially increased requirements over the last 20 years. Our study shows that “procedures” in oncology phase I trials have substantially increased over the last two decades. Prior studies have shown an annual growth rate of 6.5% in procedures per protocol across all therapeutic areas between 1999 and 2005 [11]. Getz et al. described that phase I studies had the highest overall level of procedural frequency with an average of 5.4 times [11]. This was associated with an increase in work burden for the sites conducting the phase I trials. The significant overall increase in events and procedures in the last 20 years of oncology drug development reflects that researchers are now seeking more data from a phase I study to get an early read on safety and efficacy prior to entering the more costly later-stage of drug development. With the advent of the FDA breakthrough designation, there have been recent attempts to use focused phase I trials as a basis for accelerated drug approval.

In 2016, the average number of pharmacokinetic time points was twice when compared to 1996. This reflects an ongoing trend towards defining dose to AUC relationship, the magnitude of both inter-individual and intra-individual pharmacokinetic variability and the impact of prandial conditions on exposure. These fundamental endpoints mirror an evolving drug development field that is moving away from the traditional maximal tolerated dose (MTD) to one that seeks a more effective but less toxic dose. Furthermore, in 2016 the average number of biopsies during a phase I trial was two. Patients are also being dosed more frequently and require more scheduled tests such as functional imaging (e.g. PET scan). With increase in procedural frequency, there is more burden to the patients who are participating in these trials.

Table 1 Summary statistics for variables per year

Label	1996 *N* = 21	2006 *N* = 32	2016 *N* = 49	Total 102	Pval
Total number of procedures					< 0.001[1] *
Mean (SD)	7.1 (3.1)	11.9 (6.2)	33.4 (16.6)	21.2 (17)	
Median [Q1, Q3]	7 [5, 7]	11 [7, 15]	33 [21, 41]	15 [8, 29]	
Min, Max	3, 15	3, 26	13, 91	3, 91	
PK					0.02[1] *
Mean (SD)	16.4 (12.1)	32.9 (31.3)	33.8 (29.2)	30 (28)	
Median [Q1, Q3]	15 [10, 22]	23.5 [13.8, 42.2]	25 [17, 42]	21.5 [14, 36]	
Min, Max	0, 53	0, 156	0, 152	0, 156	
Non PK tests					0.02[1] *
Mean (SD)	6.5 (4.2)	12.2 (15.4)	12.2 (16.5)	11 (15)	
Median [Q1, Q3]	6 [4, 8]	8.5 [6.8, 13]	8 [5, 13]	7 [5, 12]	
Min, Max	1, 18	0, 91	0, 115	0, 115	
ECGs					< 0.001[1] *
Mean (SD)	1.4 (1.1)	2 (1.5)	9.1 (15.9)	5.3 (12)	
Median [Q1, Q3]	1 [1, 2]	1.5 [1, 3]	3 [2, 8]	2 [1, 4]	
Min, Max	0, 4	0, 7	0, 90	0, 90	
X-rays and CT scans					0.76[1]
Mean (SD)	2 (0.8)	2.2 (0.9)	2.4 (1.6)	2.2 (1)	
Median [Q1, Q3]	2 [1, 2]	2 [2, 2]	2 [1, 3]	2 [1, 3]	
Min, Max	1, 4	1, 6	0, 6	0, 6	
Echo, MRI and PET scans					0.005[1] *
Mean (SD)	0.2 (0.6)	1 (1.4)	1.5 (2.2)	1.1 (2)	
Median [Q1, Q3]	0 [0, 0]	0 [0, 2]	1 [0, 2]	0 [0, 2]	
Min, Max	0, 2	0, 5	0, 12	0, 12	
Molecular profiling					< 0.001[1] *
Mean (SD)	0 (0)	0.2 (0.7)	2.5 (4.4)	1.3 (3)	
Median [Q1, Q3]	0 [0, 0]	0 [0, 0]	1 [0, 3]	0 [0, 1]	
Min, Max	0, 0	0, 3	0, 18	0, 18	
Biopsies					< 0.001[1] *
Mean (SD)	0 (0.2)	0.5 (0.9)	1.9 (2.4)	1.1 (2)	
Median [Q1, Q3]	0 [0, 0]	0 [0, 0.2]	1 [0, 3]	0 [0, 2]	
Min, Max	0, 1	0, 3	0, 13	0, 13	
Medication dispensing times					0.001[1] *
Mean (SD)	6.5 (7)	11.2 (10.6)	15.1 (10.9)	12.1 (11)	
Median [Q1, Q3]	4 [3, 10]	6.5 [3, 12.5]	12 [9, 21]	9 [4, 18.8]	
Min, Max	0, 30	2, 42	1, 56	0, 56	
Outpatient tests and procedures					< 0.001[1] *
Mean (SD)	1 (1.2)	1.1 (1.8)	4.1 (3.3)	2.5 (3)	
Median [Q1, Q3]	1 [0, 2]	0 [0, 2]	3 [2, 6]	2 [0, 3]	
Min, Max	0, 3	0, 6	0, 14	0, 14	
Informed consent amendments					0.002[1] *
Mean (SD)	6.2 (2.4)	6.3 (3.3)	4.5 (1.5)	5.4 (3)	
Median [Q1, Q3]	6 [5, 7]	6 [3.8, 8]	4 [3, 5]	5 [4, 6]	
Min, Max	3, 14	1, 15	2, 10	1, 15	
Medical history and physicals					0.44[1]
Mean (SD)	4.9 (3)	5.6 (3.4)	6.6 (5.3)	5.9 (4)	
Median [Q1, Q3]	4 [3, 6]	4 [3, 7.2]	5 [3, 8]	5 [3, 7]	
Min, Max	1, 12	2, 18	1, 30	1, 30	
Questionnaires /subjective assessments					0.01[1] *
Mean (SD)	0 (0)	0.25 (0.84)	1.76 (4.78)	0.92 (3)	
Median [Q1, Q3]	0 [0, 0]	0 [0, 0]	0 [0, 1]	0 [0, 0]	
Min, Max	0, 0	0, 4	0, 30	0, 30	
Contact with patients					0.011 *
Mean (SD)	0.4 (1.4)	1 (2.8)	3.6 (6.9)	2.1 (5)	
Median [Q1, Q3]	0 [0, 0]	0 [0, 0]	0 [0, 4]	0 [0, 0]	
Min, Max	0, 5	0, 11	0, 32	0, 32	

Statistically significant differences are indicated (*P < 0.05). All statistical tests were two-sided

1. Mann-Whitney U test

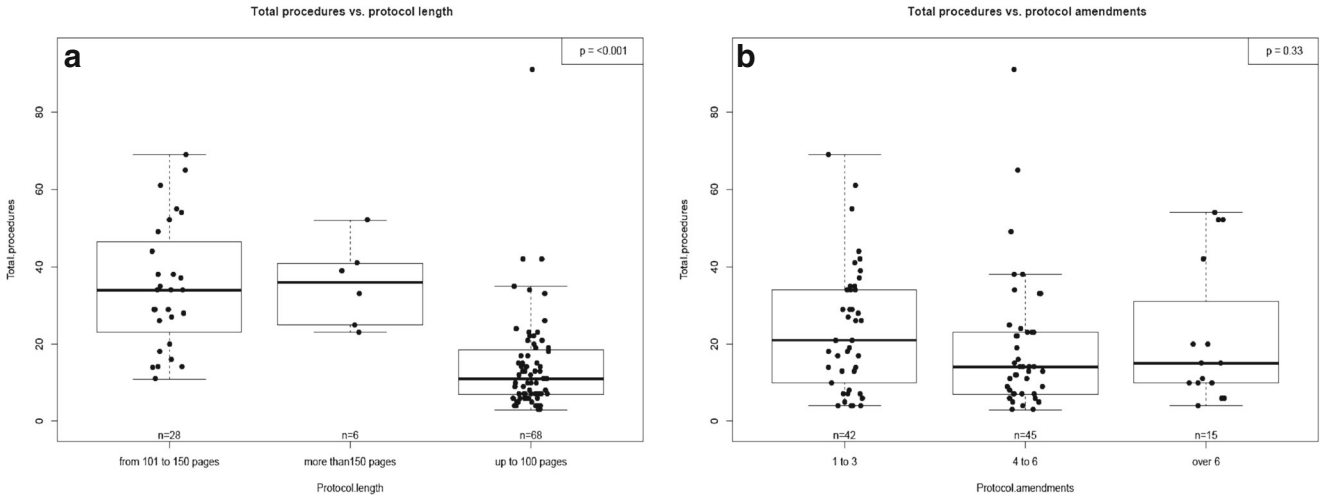

Fig. 1 Number of (a) procedures by protocol length and (b) protocol amendments: Those studies with more than 100 pages per protocol had higher median number of procedures compared to shorter protocols. The number of amendments per protocol did not correlate with procedure amounts

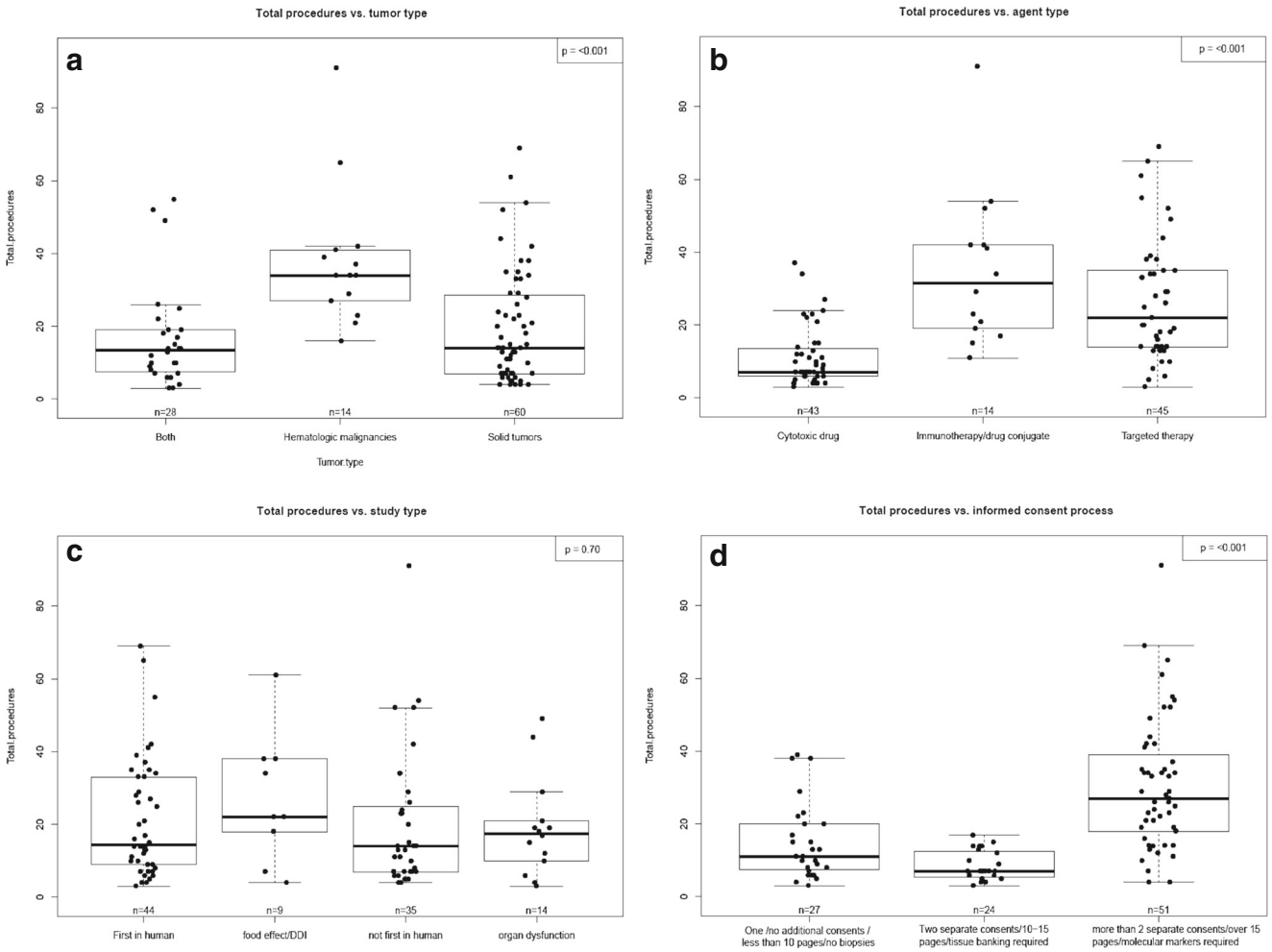

Fig. 2 Number of procedures by (a) tumor type, (b) agent type (c) study type and (d) length of the informed consent. The total number of procedures per protocol in all studies evaluated was more significant on studies of hematologic malignancies, immunotherapies or with a longer consent. However it did not correlated with the type of phase 1 study (Fig. 1c). Mean, medians, minimum and maximum of all of the data. Statistically significant differences are indicated (*$P < .001$)

In order to align reimbursement based on trial complexity and in accordance with the Clinical Trials Working Group (CTWG) Operational Efficiency Initiative, the National Cancer Institute (NCI) developed a scoring system in 2009 [12]. However, this is no longer being implemented for unknown reasons. In an attempt to quantify how protocol complexity places additional burden on study staff, The Clinical Research Associates (CRA) Committee of the National Cancer Institute of Canada Clinical Trials Group, carried out a multicenter study. This measured trials' task time and the effect of certain factors, suggesting that Industry-sponsored studies and early phase studies had significantly higher overall mean times than cooperative group studies or phase III trials [9]. Further efforts on assigning acuity level or numeric weight to cancer clinical trials reflecting complexity and intensity of care are needed. An acuity-based measurement tool will be useful to determine actual workload and direct hiring decisions [13]. There has been an overwhelming interest to address concerns related to workload in clinical trials [14]. Previous efforts were not phase I specific, captured all phases of drug development and were conducted in a different era. We need a modern and specific oncology phase I tool that is able to capture an ever increasing complexity in early drug development.

Our study has some limitations. The cross sectional sampling prevents us from determining an actual growth rate over 20 years and our conclusions are based on a limited sample size. Nevertheless, these findings provide evidence that phase I oncology trials are becoming complex with increased procedural frequency. Further research is needed to assign a unit of measure that can better allocate resources and personnel to each different protocol, expediting timelines and minimizing costs.

Compliance with ethical standards

Grant support Nil

Conflict of interest None to declare. All authors had full control of all primary data, which are available for review upon request.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Welfare of animals This article does not contain any studies with animals performed by the authors.

Informed consent Not applicable.

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