

Brief Communication

Early-phase clinical trials in the pandemic era: a four-year experience from an academic cancer center

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Abstract: Early-phase clinical trials are the first step in cancer drug development. However, they are becoming difficult to conduct - increased complexity of treatments, multiple stakeholders, and most importantly, the changes imposed by the COVID19 pandemic. We report our experience during and since the pandemic, focusing on early-phase clinical trials for solid tumors. From 2020-2023, our accruals improved by 161% (from 33 to 86). We consented 260 patients; of those, 176 (68%) fulfilled all eligibility criteria and started therapy - trials included immunotherapy (74, 42%), targeted therapy (43, 24%), novel molecules (30, 17%), cellular therapy/oncolytic viruses (19, 11%), and pharmacokinetic assessment trials of standard therapies (10, 6%). We increased staffing from 4 to 12 over this period, instituted hybrid work policies, created a dedicated triage nurse to reduce screen failures, and developed disease-specific sub-teams for better efficiencies and lower error rates. These efforts allowed us to improve the quantity and quality of our accruals.

Keywords: Clinical trial, phase 1, oncology, academic cancer center

Introduction

Early-phase clinical trials are the first step in cancer drug development. Modern designs allow rapid dose finding with small sample sizes [3], minimizing exposure to toxic doses, and hopefully providing faster access to efficacious doses, which is the primary goal of patients enrolling to such trials [2]. However, they are becoming difficult to conduct [2], with increasing costs and timelines [1, 6]. This is due to various reasons - increased complexity of treatments (novel immunotherapy agents, cell therapies, etc.), more procedural requirements (serial biopsies), multiple stakeholders (increasingly, smaller biotech companies, contract research organizations), and most importantly, the changes imposed by the COVID19 pandemic (travel barriers, remote work, shipping constraints, severe staffing shortages/turnovers). The critical elements of a successful

early-phase program are multi-faceted: a robust portfolio with adequate enrollment slots for patients in need; maintaining relationships with CROs, sponsors, and referring physicians; and keeping up with accrual goals, data quality timeliness, and regulatory requirements. In addition, the advent of more complex intravenous immunotherapeutic and cellular therapy agents for solid tumors have required increase coordination and logistical planning for such treatments. We report our cancer center's experience during the pandemic and thereafter.

Methods

The Experimental Therapeutics (ET) program at the University of Cincinnati Cancer Center focuses on early phase clinical trials for patients with solid organ malignancies. Starting in early 2020, we had plans to improve the quantity of

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accruals and the quality of our processes. However, the COVID-19 pandemic required significant changes to maintain and then grow our program. We instituted hybrid work policies to allow better retention and work satisfaction for research team personnel. For clinical trial startup and monitoring activities, we instituted remote options and eventually evolved to hybrid options to minimize delays. Further, after noticing an uptick in screen failure rates, we appointed an experienced research nurse as the intake coordinator, to field all internal and external referrals, and prescreen the patients to allow efficient scheduling and consenting, as well as early identification of reasons for ineligibility, thereby decreasing screen-failure rates after consents. Due to the increased efficiencies resulting from this role, a second intake coordinator was added in late 2023, allowing for cross coverage and specialization by tumor types and physicians. We also opened trials with a focus on potentially high-accurring studies, based on our patient population, by implementing a more robust internal feasibility assessment as well as accrual thresholds for new studies. The feasibility assessment was built on using up-to-date data on patient volumes for each cancer (some changes in our disease-focused investigator panel and evolution of referral patterns meant that traditionally high-accurring diseases were replaced by some others). We also instituted higher accrual thresholds - very rare populations (such as NTRK fusions) were no longer our focus - in order to aid in strategic selection of high accruing studies. In 2023, we also implemented a dedicated standard operating procedure for coordinating inpatient care for patients enrolling on bispecific antibody and cellular therapy trials. Most importantly, we recruited aggressively: we increased clinical research coordinators from 2 to 7 over the span of these four years, and increased data, regulatory, and clinical assistant personnel from 2 to 5.

To study the impact of these changes, we evaluated program performance metrics. Data were collected under an Institutional Review Board-approved retrospective review protocol and collated from our clinical trials database as well as curation of electronic medical records. The last follow up was in February 2024, when the database was locked. All analyses were conducted in SAS (univariate, freq, and lifetest procedures,

with statistical testing, were used); descriptive results are provided. Time estimates start from day of consent on trial; patients alive or on treatment were censored at time of database lock.

Results

From 2020 to 2023, spanning four full calendar years, a total of 260 patients were consented to 49 early-phase clinical trials. In 2020, there were 33 enrollments (to 11 different trials), which increased to 72 and 69 in 2021 and 2022, and increased further to 86 (to 20 different trials) in 2023. Enrolled patients had a median age of 62 years, with 133 (51%) males, and 225 (87%) Whites. Index cancer diagnoses included colorectal cancer (57, 22%), head and neck (31, 12%), pancreatic (30, 12%), melanoma (25, 10%), lung (22, 8%), glioblastoma (16, 6%), and others (including Ovarian, Cervical, Appendiceal, Breast, Merkel Cell Carcinoma, Leiomyosarcoma, Esophageal, Prostate, Duodenum, Glioma, Carcinoma of Unknown Primary, Uterine, Lymphoma, Liposarcoma, Thyoma, Jejunal, Angiosarcoma, Urothelial, Chordoma, Gastric, and Hepatocellular). The median time from cancer diagnosis to enrollment on trial was 24.2 months. Of the 260 patients, 176 (68%) fulfilled all eligibility criteria after screening and started trial therapy. Eligibility rates were 73%, 57%, 62%, and 79%, for the years 2020-2023, respectively. The median time from consent to treatment initiation was 19 days (range 0-80). This did not change appreciably during the four years. Major reasons for ineligibility (84, 32%) were lab abnormalities (32, 38%), performance status (16, 19%), and comorbidities (13, 14%). For the 176 patients who started treatment, the category of treatment was immunotherapy (74, 42%), targeted therapy (43, 24%), novel molecules (30, 17%), cellular therapy/oncolytic viruses (19, 11%), and pharmacokinetic assessment trials of standard therapies (10, 6%). Time from consent to start of treatment was notably shorter for pharmacokinetic trials, as expected (**Table 1**). The trial treatment regimens included a median (range) of 2 (1-6) drugs. Of the 176 patients, 103 (59%) patients experience at least one grade 3 or higher adverse event (AE), with a median (range) of 1 (0-7) per patient, for a total of 239 such AEs in the study population. The most common AEs

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Table 1. Key characteristics of patients who started clinical trial treatment

	IO (n=74)	TT (n=43)	NM (n=30)	CT (n=19)	PK (n=10)	Total (n=176)
Most common index cancer	Colorectal (20, 27%)	Colorectal (14, 33%)	Cutaneous (10, 33%)	Cutaneous (10, 53%)	Glioblastoma (5, 50%)	Colorectal (39, 22%)
Median days, consent to treatment	19	19	21	22	9	19
Any Gr ≥ 3 AE	46 (62%)	26 (60%)	18 (60%)	11 (58%)	2 (20%)	103 (59%)
≥ 4 Gr ≥ 3 AEs	8 (11%)	6 (14%)	0 (0%)	3 (16%)	0 (0%)	17 (10%)
Disease control rate	19/59 (32%)	15/36 (42%)	16/26 (62%)	7/18 (39%)	1/2 (50%)	58/141 (41%)
Median months on trial	2.65	1.55	3.11	3.37	1.55	2.77

IO: Immunotherapy; TT: Targeted Therapy; NM: Novel Molecule; CT: Cellular Therapy (includes oncolytic viruses); PK: Pharmacokinetic Trial; Gr: Grade. "Cutaneous (includes melanoma and squamous cell skin cancer)". For disease control rate, denominators include only patients who reached the first response assessment timepoint.

were lab abnormalities (18%), pain (12%), infection (11%), gastrointestinal disorders (11%), and respiratory problems (8%). While not statistically significant, novel molecule therapy trials were associated with fewer adverse events compared with other treatment categories (**Table 1**). Of the 176 patients, 141 (80%) reached the first disease assessment time-point: 20 (14%) had partial response, 38 (27%) had stable disease, and 83 (59%) had progressive disease. Of note, those on novel molecule studies had a higher numerical disease control rate, although differences were not statistically significant, likely due to small numbers in each group (**Table 1**). The vast majority of patients (130, 81%) stopped the study due to eventual progression of disease. Overall, 121 (69%) have died, 41 (23%) are off study and alive, and 14 (8%) are on trial at last follow-up. Median time on trial was 2.77 months; median overall survival was 7.47 months. These were not remarkably different between the various treatment categories (**Table 1**). The above findings reflect the feasibility of conducting early phase clinical trials during and since the COVID-19 pandemic. Despite the various logistical barriers, we increased enrollment, lowered the screen failure rate, increase the complexity of clinical trials, maintained rapid consent to treatment timelines, and continue to expand the diversity of clinical trials in terms of cancer diagnoses, treatment options, and patient demographics.

Discussion

Early-phase clinical trial programs are inherently heterogeneous, influenced by patient populations, oncologists' research interests, and traditional referral pathways. Our results demonstrate that, despite these challenges, our program has successfully adapted to the evolving landscape of early-phase trials, including the disruptions imposed by the COVID-19 pandemic. These findings align with previous reports [4, 5, 7, 8] emphasizing the importance of strategic adjustments in trial operations to maintain productivity and quality.

Adapting to pandemic challenges

The COVID-19 pandemic presented unprecedented logistical and operational barriers to early-phase clinical trials, including travel restrictions, staffing shortages, and increased

procedural demands. To navigate these challenges, we implemented a multi-pronged strategy focusing on hybrid work policies, enhancing staffing levels, and streamlining processes. Hybrid work arrangements proved instrumental in improving staff retention and satisfaction, which in turn supported trial continuity and higher patient accrual rates. Our recruitment efforts - expanding the clinical research coordinator team from 2 to 7 and increasing support staff - underscored the necessity of investing in human resources to sustain trial operations during such crises.

Enhancing screening and enrollment efficiency

To address increased screen failure rates, the appointment of an experienced research nurse as an intake coordinator significantly improved pre-screening processes, reducing ineligibility after consent and enabling efficient patient scheduling. The addition of a second intake coordinator in 2023 further refined these processes, allowing specialization by tumor type and enhancing cross-coverage. These targeted interventions resulted in steady improvements in eligibility rates, rising from 57% in 2021 to 79% in 2023, and contributed to the overall increase in patient enrollments over four years.

Expanding trial portfolio and complexity

Strategic changes in trial selection criteria, such as focusing on high-accruing studies and reevaluating the feasibility of rare-disease trials, enabled us to better align our portfolio with patient needs. We increased the number of trials from 11 in 2020 to 20 in 2023, covering a broader range of cancer types and therapeutic categories. The addition of a standard operating procedure for inpatient coordination of complex treatments, such as bispecific antibody and cellular therapy trials, reflected our commitment to managing increasingly intricate protocols.

Clinical outcomes and future directions

Our retrospective analysis demonstrated the feasibility of conducting early-phase clinical trials even amidst the challenges of a global pandemic. We successfully increased enrollment, reduced screen failure rates, and maintained rapid consent-to-treatment timelines. Adverse event rates were consistent with expectations,

with no untoward signals or increase in frequency with increasing enrollment - reassuring that higher quantity of accrual did not sacrifice quality of care or patient selection. Further, while overall survival metrics remained consistent across treatment categories, the higher disease control rates observed in novel molecule trials highlight their potential for further investigation. Findings reaffirm the value of early-phase trials in advancing cancer research and improving patient outcomes.

In conclusion, our experience underscores the critical elements of a successful early-phase clinical trial program: adaptive operational strategies, robust recruitment efforts, integration of technology, and a commitment to inclusivity and patient-centric care. Moving forward, these principles will remain central to our efforts in optimizing trial operations and contributing to the broader landscape of cancer drug development.

Disclosure of conflict of interest

DS reports prior or active roles as a consultant for Elevar, Regeneron, AstraZeneca, Replimune, Cancer Commons, TransThera, Totus Medicines, and Valar Labs; prior or active Speaker Bureau roles for AstraZeneca, Incyte, and Seagen; and received research grants from Aadi, Ability Pharma, Amgen, Apexigen, Astellas, AstraZeneca, Bexion, Bristol-Myers Squibb, FibroGen, Genentech, Hengrui, Merck Mirati, NextCure, PanCAN, Regeneron, Roche, and Triumvira.

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