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Academic Cancer Center Phase I Program Development

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ABSTRACT

Multiple factors critical to the effectiveness of academic phase I cancer programs were assessed among 16 academic centers in the U.S. Successful cancer centers were defined as having broad phase I and I/II clinical trial portfolios, multiple investigator-initiated studies, and correlative science. The most significant elements were institutional philanthropic support, experienced clinical research managers, robust institutional basic research, institutional administrative

efforts to reduce bureaucratic regulatory delays, phase I navigators to inform patients and physicians of new studies, and a large cancer center patient base. New programs may benefit from a separate stand-alone operation, but mature phase I programs work well when many of the activities are transferred to disease-oriented teams. The metrics may be useful as a rubric for new and established academic phase I programs. *The Oncologist* 2017;22:369–374

INTRODUCTION

Phase I cancer clinical trials evaluate investigational agents being used for the first time in humans. In the twentieth century, phase I studies were designed to define the relationship of agent dose and schedule to toxicities. Interpatient dose escalation and alternate schedules were examined. Maximal tolerated dose (MTD), recommended phase II dose (RP2D), dose-limiting toxicities (DLTs), and pharmacokinetics (PK) were assessed. This approach was nonspecific as most anticancer agents were cytotoxic drugs that inhibited DNA synthesis or mitotic spindles targeting cell proliferation [1], and higher doses were associated with a narrow therapeutic index—greater toxicity and efficacy. However, cancer therapeutics in the twenty-first century has focused on the introduction of targeted agents that specifically target tumor antigens or modify tumor, stroma, or immune pathways. These new agents may not require achievement of MTD or DLT to achieve maximal antitumor efficacy. Instead, lower doses sufficient to modulate the target optimally may yield maximal therapeutic gain. Consequently, recent phase I trials include dose selection, correlative assessments

of potential tumor biomarkers, pharmacodynamics, and/or metabolic imaging to demonstrate proof-of-mechanism. Expansion cohorts of patients are added to better define toxicities, drug distribution and metabolism, mechanism of action, and preliminary evidence of drug efficacy in specific tumor types.

These changes have significantly altered the classical phase I programs. The studies are more complex and labor-intensive and tax the resources of many institutions. Phase I studies are also used earlier in the treatment course and, combined with their greater efficacy, lead to patients remaining on studies longer, adding significant coordinator effort. Nevertheless, such phase I trials may accelerate drug development and enhance the potential for clinical benefit. The detailed correlative studies can inform academic and industry research objectives. The individualized treatment, based on the patient's tumor biology, may lead to an improved therapeutic index and provide additional opportunities to improve individual clinical outcomes as well as societal gain. There are >700 new phase I oncology trials per year [2]. Each costs millions of dollars and

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necessitates an organized and efficient clinical research infrastructure [3].

In this review, we analyze a set of parameters associated with specific disease types, research sites, patient populations, and the compound classes that play an important role in the development of an early phase therapeutics program. We have explored various factors that can reduce barriers to the establishment of a successful phase I program in the setting of academic or community cancer centers. In addition, we offer recommendations that can enhance the experience of participating in a phase I program for patients, caregivers, investigators, institutions, and local communities. Areas that have been addressed include program organization, personnel, facilities, regulatory issues, formal meetings, study properties and logistics, patient accrual and enrollment, financial elements, philanthropy, and other institutional commitments necessary to initiate and conduct a successful phase I program. We report findings from 16 cancer-focused phase I centers—all university-based. Results from these measurements were compared with the phase I programs' outcomes, including number of active studies, the properties of the studies, and the number of patients enrolled on different types of studies.

INSTITUTIONS AND METHODS

One- to two-day site visits and/or phone interviews were conducted in 2016 with City of Hope, Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center, University of Texas San Antonio Cancer Treatment and Research Center, University of Alabama Birmingham Comprehensive Cancer Center, Holden Comprehensive Cancer Center at the University of Iowa, Medical College of Wisconsin Cancer Center, University of Arizona Cancer Center, University of Michigan Comprehensive Cancer Center, Massachusetts General Hospital Cancer Center, Vanderbilt-Ingram Cancer Center, Georgetown Lombardi Comprehensive Cancer Center, OHSU Knight Cancer Institute, University of Washington Fred Hutchinson Cancer Research Center, Washington University School of Medicine Alvin J. Siteman Cancer Center, Barbara Ann Karmanos Cancer Institute, and the Harold C. Simmons Comprehensive Cancer Center at the University of Texas Southwestern.

Each site was analyzed using the metrics in the supplemental Tables 1–5. For overall organization, we evaluated whether the phase I program was integrated or separate, whether there was a designated phase I Director and Associate Director, the number of phase I principal investigators, and the administrative reporting structure for the phase I staff. Personnel assessed included the number of phase I dedicated coordinators, regulatory and contract personnel, blood and tissue sample handling/processing/shipping team members, social workers and financial counselors, investigational pharmacists, administrative assistants, and budget/financial analysts. For facilities, we judged whether there was dedicated phase I space and whether the exam rooms, infusion rooms, pharmacy, pharmacology lab, and offices were nearby. Because regulatory issues can have a significant impact on the success of a phase I program, we weighed available phase I standard operating procedures (SOPs)—SOP documents, Data and Safety Monitoring Committee (DSMC) tolerance for phase I minor deviations, the presence and number of phase I regulatory staff (particularly those with U.S. Food and Drug Administration [FDA]

experience), the experience with internal and external audits, and the opportunity of the phase I director to meet regularly with the Protocol Review and Monitoring Committee (PRMC), DSMC, and institutional review board (IRB). Phase I meetings to review serious adverse events and prioritize trials and patient accruals were noted, and meeting frequency, member participation, and meeting location were gauged. In addition, formal meetings of the phase I director with cancer center leadership and with phase I staff were examined.

The study characteristics were rated, including average time to study opening, average number of sites per study, number of hematology and organ-specific trials, number of broad-spectrum solid tumor trials, number of institutional or investigator Investigational New Drug (IND) documents, and number of investigator-selected trials (ISTs). Patient issues that facilitated study entry were estimated, such as the average time from patient referral to signed informed consent, presence of institutional tumor genomic profiling, participation in community minority and general outreach talks, institutional marketing of phase I trials, and available funds for patient travel and lodging. Financial matters were addressed and included phase I philanthropy, institutional trial startup costs, institutional overhead, and maintenance of phase I billing/spreadsheets. The overall institutional properties and commitment to phase I were benchmarked by institution patient base, National Cancer Institute (NCI) funding, philanthropy assistance, basic science collaborations, and personnel turnover. Finally, we approached program specialty issues—available Good Manufacturing Practices facilities, advanced imaging, molecular marker assay, multimodality trials, and presence and nature of assistance in protocol preparation, such as written guides [4].

The definition of a successful phase I program varies with the needs of the institution and the community. Rapid access to a variety of new agents for a large patient population was regarded as important for most communities and caregivers. Endpoints included number of trials and patients treated per year. The addition of novel science and institutional therapy discoveries was ranked highly at academic centers with significant translational research and/or basic science reputation. Endpoints measured included average number of sites/trial, number of ISTs, and number of patients treated on ISTs. We embraced features important for both community and academic medicine in our rubric.

STATISTICAL ANALYSIS

Characteristics of the cancer center phase I trial programs were described using descriptive statistics, such as frequency and percentage for categorical variables, mean and standard deviation for continuous variables with symmetric distribution, and median and quartiles for continuous variables with skewed distribution.

RESULTS

Findings are shown in the supplemental online Appendix and supplemental online Tables 1–5. We masked the identity of each program and provided information only for the individual site for the appraisal. Because of the challenges of covering all the different programs with a single set of metrics, summary descriptive paragraphs were given. Details of the findings at

each site are described in the Site Summary Text of the supplemental online Appendix.

DISCUSSION

Analysis of multiple successful cancer center phase I programs revealed surprises regarding organization, personnel, and facilities and anticipated importance of elements in regulatory management and trial selection. These observations may permit others to avoid discovery by trial and error.

There were three major methods of site organization—total, basket, and integrated. The total program had all phase I studies treating patients with one type of malignancy, patients with different neoplasms with defined genetic drivers or molecular markers, and patients with any solid tumor or hematologic malignancy. The basket program left disease-specific phase I trials to disease-oriented teams and only handled studies that enrolled patients with multiple cancer types. Finally, the integrated programs had no separate phase I personnel. All phase I work was done with the physicians and personnel of different disease-oriented teams. If multiple tumor types were eligible for a study, one disease team managed the protocol and led the study and activities.

The benefits of a total program were dedicated, experienced personnel and facilities that were best able to address the regulatory, monitoring, and pharmacologic complexities of phase I studies. Total programs avoided duplication of early phase financial, regulatory, and administrative services. The negative aspects included patient recruitment difficulties. To recruit patients, the phase I personnel had to approach physicians and patients in various disease-oriented care teams. Patients may be hesitant to transition to a new physician. There may be very limited or no routine interaction with the disease-oriented team or patients pre- and post-study. In addition, there were extra personnel/facilities costs and discontinuous patient care. When we began this review, our expectation was that total phase I programs would have multiple benefits that would become apparent in terms of trial numbers, patient recruitment, ISTs, and investigator mentoring. With one exception—site #14—that did not turn out to be the case. Evaluated institutions with basket or integrated phase I programs had more median phase I trials, phase I patients, phase I ISTs, and dedicated principal investigators (PIs) compared with total phase I programs. Cancer centers with new or smaller experimental therapeutics may benefit from trained physician leaders and staff dedicated to phase IA/IB activities. However, our data suggested mature and larger phase I programs were highly effective with the phase I activities managed by individual disease-oriented teams—particularly with experienced research staff.

Staffing includes screening and treatment coordinators, data managers, and research nurses. We anticipated that the long hours and aggressive pace of phase I patient care and data management would tax the staff and that higher ratios of staff to trials would be associated with higher patient accruals. Again, we were surprised to find that was not the case. The number of trials per coordinator/nurse ranged from 0.9 to 18, and there was no correlation with total patients accrued. In fact, the highest enrollments were at sites with a median of 3–7 trials per coordinator/nurse. Sites #5, #11, #13, and #16 were outstanding outliers with 6.9, 15, 18, and 12 trials per coordinator/nurse and 89, 304, 173, and 118 enrolled phase I patients

in 2015–2016, respectively. Factors other than numbers had an impact on productivity. Sites #5, #10, and #11 had direct coordinator/nurse supervision by the physician leader versus a clinical research organization matrix model. Site #5 physician leader met to review patients with staff for an hour daily. Sites #4, #10, and #11 physician leaders met with staff weekly for an hour. Also, sites #4, #5, and #10 had phase I SOPs in place that required PIs to provide accurate and timely documentation on patient visits and lab/x-ray results. Sites #4 and #11 transferred studies, when they had less acuity in phase IB expansion cohorts, to disease-oriented teams. This permitted improved staff efficiencies. Staff retention was variably affected by workload. While there was no statistical association between the number of patients or trials per coordinator and percentage of staff turnover for the sites overall, the sites with the highest ratios and available information, sites #5 and #11, did have 70% and 33% staff turnover, respectively, in 2015. Site #4 doubled patient accrual in year 2 but had difficulty in recruiting research coordinators. Several sites had very low personnel turnover (0%–2%), and these sites had the most experienced phase I managers. Some programs aggressively recruited and retained experienced managers and highly qualified staff. Such activities were needed to avoid “burnout.” Staff at these sites were scientifically engaged by participation in projects and publications and given salaries and benefits packages that exceed other institutional and geographic area offers. Site #2 was plagued at first by high turnover, but instituted a “pod system” that markedly reduced staff departures. Pods had a screening coordinator, a treatment coordinator, a data manager, and a laboratory technician. Each pod handled, on average, eight phase I trials, and all pod members were familiar with the details of the eight trials. When individuals were absent due to vacation, illness, site initiation visits, or investigator meetings, there were other members of the pod who could help care for the patients, complete case report forms (CRFs), participate in teleconferences, and attend weekly phase I meetings. Four of seven sites used an acuity index to assign studies so that no single employee had the majority of complex studies. These indices are algorithms that quantify coordinator/nurse workload on a study [5]. Although SOPs, structure modifications, and acuity measures assisted in staff performance, the single most important factor was the experience and direct supervisory role of the physician leader and research manager. Site #2 underwent changes during the study. Management of personnel was transferred from a dedicated phase I physician to a core research administrative team. Regulatory and financial steps were dispersed within the institution. In the year following these changes, the number of phase I trials fell from 32 to 13 (56% reduction) and the number of accrued phase I patients went from 75 per year to 30 per year (60% reduction). As predicted from leadership studies, the quality and experience of the physician leaders and clinical research managers were the most critical factors in program employee retention and success [6, 7].

Oversight of phase I trials has an important and informative history [8]. Formalized clinical trials for safety were the consequence of the antifreeze-tainted elixir sulfanilamide and the Federal Food, Drug, and Cosmetic Act of 1938. Informed patient consent was the result of the World War II medical atrocities, resulting in the Nuremberg Code of 1947, the Declaration of Geneva of 1948, the Helsinki Declaration of 1964, and

the Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act of 1963. The IRB, required for review of patient risks and benefits in clinical trials, followed the Tuskegee syphilis study and the Belmont Report of 1979. Finally, Good Clinical Practice (GCP) guidelines and CRFs were mandated after the International Conference on Harmonization in 1996 [9].

With this history, institutions have built large infrastructures to ensure clinical research compliance. For efficient analyses of phase I protocols, deviations, modifications, and periodic reviews, close communications between the institutional regulatory bodies and PIs is essential. Our survey confirms this. Sites #3, #4, #6–#10, #12, #14, and #16 had regular meetings with the PRMC, IRB, and in some cases, the DSMC, and had the shortest times from protocol submission to patient enrollment. We cannot emphasize enough the value of an active and frequent dialogue between phase I PIs or physician leaders and the regulatory bodies. Paper and electronic submissions fail to yield maximal and timely information exchange. We recognize the difficulties of this discourse when IRBs handle hundreds of studies, including many that are phase II–III or not cancer-related. Two of the three local regulatory bodies, PRMC and DSMC, have vague mandates. The NCI requires “scientific review” of trials by the PRMC. The changes suggested by the PRMC were implemented in 40% of ISTs and 5% of industry studies [10]. In the end, 97% of industry-sponsored trials and 90% of investigator-sponsored trials were approved by the PRMC. This again supports early and frequent communication with the regulatory body. DSMCs have a more diffuse role in phase I and II trials. With the aid of statisticians and community members, they address safety and data quality on an ongoing basis during the study. Industry generates their own DSMCs, but investigators use the institutional DSMC for ISTs. Details of their operation are distinct for each organization. Some focus on safety and others on data quality [11–15]. Available DSMC plans include those by the National Institute of Dental and Craniofacial Research (<https://www.nidcr.nih.gov/Research/ToolsforResearchers/Toolkit/DSMBGuidelines.htm>), and the University of Oregon, the University of Wisconsin, and the Dana-Farber Cancer Institute, among others (<https://cancercenters.cancer.gov/>). Because each institution's DSMC has its own priorities, again, close communication and cooperation between the phase I physician leader, phase I manager, phase I quality assurance personnel, and DSMC is vital. DSMCs can place studies on hold for safety or data quality. In fact, the DSMCs of 4 of the 16 sites permit no deviations from protocol (sites #2, #7, #8, #11, and #12), whereas the other 12 of the 16 sites evaluate deviations on a case-by-case basis. Deviations triggered a protocol hold only at site #2. A fourth regulatory oversight body is the FDA. Investigator-initiated or -sponsored trials require IND submissions and FDA notification of serious adverse events (SAEs) within 15 days, according to the Code of Federal Regulations 21.312.32. IST PIs and phase I regulatory personnel must be aware of their federally mandated obligation to notify the FDA promptly. All the regulatory issues in phase I can be summarized in one word—communication.

Nevertheless, for all sites, delays in trial activation were the most consistent and strong theme to emerge from this review. Barriers were multifactorial but likely augmented by large and often redundant regulatory bodies [16]. Published data indicate that longer time to trial activation is associated with lower

patient enrollment [17]. At site #9, a fast-track program was developed that reduced study initiation time from 163 days to 45 days [18]. Site #4 embedded dedicated financial, regulatory, and grants/contract officers to improve trial activation times. Site #2 went in the opposite direction with transfer of management, regulatory, and financial matters to activities outside the phase I program, leading to a prolongation of study activation time from a median of 5 months to greater than 12 months and a two-thirds reduction in phase I trials and accrued patients in the next year. Sites #9 and #14 had the shortest startup times and the most phase I trials and ISTs and IST patients accrued and were among the top three sites for overall phase I patient accrual. Thus, we strongly believe GCP and institutional compliance can be maintained with a smaller, streamlined bureaucracy and such institutional changes will positively impact phase I programs.

Study content is the “meat” of a phase I program. We identified four types of phase I trials—phase IA, phase IB, phase I trials with institutional correlative science, and ISTs. Phase IA trials are first-in-human dose-escalation studies. Phase IB trials expand the number of patients treated at the MTD in a novel disease cohort or combine the drug with a second therapy in a limited dose-escalation schema. Correlative science phase I trials use institutional experimental laboratory or imaging biomarkers. ISTs are based on investigator science or clinical research and may use locally generated agents. There is often an evolution of trials at sites. New programs are often selected to participate in phase IB studies. Physician leaders and PIs can make connections to the pharmaceutical/biotechnology industry or contract research organizations to gain access to these studies. The phase IB trials typically have multiple sites and reduced PK assays and SAEs. The study may be an expansion in particular diseases based on phase IA or pharmacogenomics. Most consist of pathway inhibitors or immune checkpoint modulators in disease subsets or combinations of pathway inhibitors or immune checkpoint modulators with members of the same therapeutic class or other agents. Sites #3, #4, #6–#13, #15, and #16 had many of these studies and had excellent patient accruals. Sites #2, #6, #7, #10, and #15 are relatively new phase I programs and have benefited from this class of clinical study. Retrospective analyses of patients treated on primarily phase IB studies for gastrointestinal cancer and lung cancer showed response rate (RR) of 4% and 16% and stable disease of 38% and 41%, respectively [19, 20]. Further, in genomically matched patients, phase I trials yielded a RR of 27% [21]. Hence, this class of phase I investigation benefits both the institution and patients. In fact, clinical genomics yielded actionable DNA alterations in 89% of prostate cancer patients in one cohort of 150 patients [22]. Phase IB trial selection based on genomics is feasible. Phase IA or first-in-human studies are more commonly performed at private practice phase I units due to speed of activation, patient volumes, and experience. They have more pharmacokinetics and pharmacodynamics and toxicity reporting. Nevertheless, several first-in-human trials were performed at some cancer center sites. Site #3 had a large PK laboratory. Site #2 had PI expertise in a particular therapeutic class. Because of their small patient volumes, their main attraction is their novelty. By participating in phase IA, if the biological activity is promising, the site is well positioned for further studies. Phase I studies with institutional

correlative science are very attractive for institutions with a large basic and translational science expertise. Site #2 used advanced magnetic resonance imaging (MRI) imaging in trials testing onco-metabolite and transcription factor inhibitors. Site #4 had access to a molecular imaging core facility with a cyclotron and positron emission tomography/MRI. Site #11 also used advanced MRI and ultrasound imaging to quantify changes in tumor perfusion as part of the phase IB studies. Site #13 performed clinical genomics prospectively on pretreatment tumor samples, which permits early identification of biomarkers. Site #14 offered serial tumor biopsies and rapid autopsies. Site #16 had many immunological assays. The requirements to perform such studies include reagent support from industry and philanthropic or grant support from the institution.

ISTs represent the pinnacle of cancer center discovery and advancement. These have the greatest opportunity for mentoring clinical investigators. Sites #1–#3, #9, #14, and #16 had the most ISTs and the highest ratio of IST/all phase I trials. In prior years, the ISTs at these sites led to first or senior author presentations at the American Society of Clinical Oncology and publication of journal articles. Patients benefited from the PI insights and the partnerships between biotech/pharma and the cancer center.

Patient accrual on trials is challenging both for getting referrals and for consent and eligibility. Navigators are extremely valuable in increasing referrals, as shown at sites #1, #3, #4, #8, #10, #11, and #14. A large patient base—17,000 new cancer patients in 2015—aided referrals for site #6. Screen failures are common and occur due to cancer progression during the screening period and/or poor performance status [23]. The Royal Marsden Hospital prognostic score has been validated by an MD Anderson Cancer Center phase I clinic [24, 25]. Multiple relapsed patients also do more poorly on phase I studies [26]. In contrast, patients with cardiac ejection fraction >35%, modest renal dysfunction, or elderly healthy patients do well on phase I trials [27–29]. Patient refusal is another barrier—African Americans and Latinos are two- and three-fold more likely to decline phase I study enrollment, respectively [30, 31]. A minority recruitment plan has been initiated at two of our phase I sites [32, 33]. Most patients lack understanding of the intent of phase I trials [34]. In addition, many oncologists do not refer patients for phase I trials due to perceived lack of clinical benefit and costs in physician time and resources [35]. In light of this heterogeneity, navigators, community and physician education outreach, cooperative group physician referral minima, and adequate patient informed consent are important and worthy of the time, resources, and effort [36, 37]. One site added prescreening, frequent communications with patients, dedicated staff to interact with insurance providers, and social media/patient advocacy group engagement to enhance trial accrual [18]. Phase I trial patient enrollment is the single most challenging aspect of phase I program growth.

Our review did not address private U.S. phase I centers and international academic phase I programs. We approached two private phase I businesses, but neither was willing to provide infrastructure information. Many of the challenges observed in academic centers may be streamlined in non-university environments, but the role of ISTs and pharmacodynamics studies

may be more difficult without institutional basic science. International academic centers were not studied due to cost and time constraints but merit evaluation and comparison. Govindan and colleagues compared various oncology clinical research parameters between Washington University of St. Louis (one of our sites) and the University of Torino, Italy [38]. The median time to trial opening and median number of patients accrued per study was 5.5 months and 7.4 patients, respectively, for the U.S. university versus 3.7 months and 37 patients, respectively, for the Italian university. Their analysis found multiple additional steps and longer time to activate trials in the U.S. In addition, insurance denials reduced patient accruals in the U.S. but not in Europe, with socialized medicine. Future detailed studies are warranted to learn from U.S. private and European academic phase I programs.

CONCLUSION

Phase I programs merit careful consideration of size and expansion goals and endpoints. Based on the nature of the institution and community and local physician networks, there are multiple choices. Cancer centers serving large populations with large private practice oncology groups may be served best by phase IB studies yielding enhanced safety and some efficacy and a more robust trial portfolio. Cancer centers with an active pharmacology department are ideal sites for phase IA and correlative science experiments [39–42]. Basic research-rich universities and translational research centers may focus on ISTs and institutional INDs. Finally, new phase I programs may progress from phase IB to phase IA/correlative science studies toward ISTs over time as more resources are available and as the site's reputation grows. The logistical support to achieve high-quality care and research is a tremendous undertaking and must address management, personnel, regulatory, patient education, and navigation [43, 44]. In summary, we strongly believe the complex efforts for phase I programs are worth nurturing, provide an outstanding service to cancer patients, can lead to improved human health, and can lead to advancements in science in many cancer centers.

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