In The Phase 1 Setting

Cancer is a disease of the aging population. According to the Canadian Cancer Society, 43 per cent of new cancer cases and 60 per cent of deaths due to cancer occur among those who are at least 70 years old.1 As Canadian baby boomers continue to age, the percentage of seniors in our society will increase from 13 per cent in 2005 to 23-25 per cent by the year 2031. This shift in demographics will be accompanied by a significant increase in the incidence of cancer.

In response to the anticipated growing need for cancer treatments, the bio-pharmaceutical industry has turned much of its attention to the continued development of drugs in this therapeutic area. Approximately, 25 per cent of all compounds being researched are those destined to treat cancer and their clinical development is said to represent in excess of $800,000,000 U.S. per compound.2

The many challenges of oncology drug development are as complex as the disease itself. This article will provide a brief overview of targeted cancer therapy and discuss certain challenges to their development, as they relate to the Phase I clinical development setting. Finally, a unique opportunity will be presented that serves to support the efforts of industry and clinicians alike.

Targeted cancer therapies

Targeted cancer therapies are currently being developed to respond to a need for more effective treatments producing fewer side effects. These therapies consist of drugs or other substances that may interfere with certain cell signalling pathways or cell receptors involved in cancer cell division, which in turn, block the growth and progression of cancer. It is thought that these compounds may be more effective than other types of treatment, such as chemotherapy and radiotherapy, and less harmful to normal cells by focusing on molecular and cellular changes that are specific to cancer. Most targeted therapies are either small-molecule drugs, able to penetrate cells and target certain cell pathways, or humanized monoclonal antibodies that target certain receptors at the cell surface.
Clinical Development Challenges

Phase I clinical trials in all therapeutic areas serve to profile a research drug's safety and tolerability. This information leads to establishing the maximum tolerated dose for humans. However, unlike Phase I studies in other therapeutic areas, Phase I oncology trials are conducted in patients as opposed to healthy volunteers, since administering cancer drugs to healthy subjects is considered unethical. Phase I oncology trials are usually reserved for patients who have failed prior treatment therapies and who do not have other viable treatment options. Many early Phase trials combine targeted therapies with chemotherapeutic agents which have greater likelihood of causing adverse side effects.

The patient population participating in these trials has a higher risk of experiencing these effects because of their compromised physical status. This makes understanding the source of side effects harder and subsequently, adds to the complexity of establishing a maximum tolerable dose. Although the clinician maintains the ultimate responsibility for assuring patient safety, the company medical representative, who is also a physician, is the one who masters all pre-clinical and clinical data on the compound. Together, they discuss causality related to side effects and the company medical representative then determines if it is safe to escalate the dose within a new cohort. If it is, then a new set of patients is recruited. This type of stepwise dose escalation is typical to Phase I trials. Besides managing dose escalation safety issues, managing the cohorts or patient groups themselves is yet another challenge. Patients are enrolled in groups of three at a specific dose and repeatedly administered the research compound and followed to determine how well the drug is tolerated.

Unlike other Phases of clinical research where recruitment may occur as a steady flow of patients, recruitment in Phase I trials is dependent on a “safety” green light. Typically there are anywhere from three to five clinical research sites participating and before an oncologist can recruit a new patient, they must first check to see if additional patients are required at a certain dose level. If not, they must wait for approval from the company medical representative to proceed. Despite the fact fewer patients are needed in phase I trials, they can take in excess of 18 months to complete due to the step-wise process.

Pharmacokinetic blood sampling, which provides valuable insight into how the drug is metabolized, is a critical component of Phase I trials. Patients have to comply with blood draws that are performed at very specific intervals throughout the course of a predetermined period. The health care team must ensure that samples are collected, processed, stored and shipped according to strict guidelines in order to ensure their integrity for analysis.

All phases of clinical research call for rigorous processes. However, because little is known about compounds in Phase I development, undetected errors are thought to have graver consequences. Therefore, processes have to be extremely well executed and documented on behalf of the clinical research teams. These systems and their documentation must then be verified and approved by an external source such as the company itself, or a third party such as a Contract Research Organization. The data collected and analysed at this stage determines whether the drug continues to move along the drug development continuum, or whether human and financial resources are reallocated to a more promising compound. Go-NO Go decisions determine the future of any given compound.

Bio-pharmaceutical industry challenges

Typically, Go-NO Go decisions are taken by biotechnology companies, as they are the key players in the conduct of early phase clinical research. Most of these companies are currently faced with significant financial constraints and therefore, lack the necessary funding to adequately support their clinical research programs. Those that have successfully accessed capital have done so through partnerships with Venture capital groups who represent the primary source of funding to the industry.

With oncology clinical drug development attrition rates thought to be fourfold higher in oncology, than in other therapeutic areas, companies are under tremendous pressure to provide investor value through sound financial and drug development management. Their strategy is to focus development efforts on the most promising drug candidates in their pipeline, monitoring closely for the first sign of success or failure. Management teams must demonstrate the ability to rapidly reallocate spending where it is best utilized and therefore, flexibility and adaptability are paramount.

Working with limited financial resources means biotechnology companies usually conduct business with a small number of permanent employees. Many of the drug development components are outsourced to Contract Research Organizations. With so much at stake, the task of delegating complex clinical activities while maintaining accountability can make for highly stressful circumstances. However, if managed successfully, outsourcing can enhance clinical performance and reduce overall costs. Each company must assess their specific needs before making outsourcing decisions, but frequently, small companies need access to core competencies part of their internal organization and often can benefit from the privileged business relationships third parties may have established.

Opportunities

Despite the multiple challenges in the clinical development of oncology compounds, it is clear that finding new and better medicines to treat cancer must remain a priority. Canadian investigators, who are known for their commitment to science and quality work, are highly motivated to participate in early phase, cutting edge clinical research. Theses trials represent an opportunity for them to contribute to the understanding of new compounds in the clinical setting. Several have access to state of the art Phase I units and a team of experts at their side.

Scimega Research, a Canadian Oncology Contract Research Organization has developed a concept to help investigators attract a greater number of cutting edge trials to Canada. The initiative, called the Reverse FeasibilityTMProgram brings a nation-wide network of qualified Phase I sites together. For investigators, the network provides their team with enhanced international exposure via Scimega Research’s team, who actively pursues business opportunities with U.S.-based biotechnology companies, which represents the largest biotechnology hub in the world. Investigators are given the opportunity to further showcase their team’s expertise and to communicate areas of interest related to clinical research. The ultimate goal is to help clinicians attract studies, for which their site currently lack clinical trial activity. This is a novel and efficient way of placing trials.

Traditionally, companies either approach investigators directly or mandate a Contract Research Organization with the task of contacting a list of investigators to discuss a specific trial. The hope is that the proposed study arrives at an opportune time where offer and demand intersect. However, the success rate is variable, and the experience can be time consuming and frustrating for both parties, as companies need to move their timelines along quickly to contain costs. This also leaves investigators with limited time to devote to fruitless queries, while patients are waiting in the wings.
The prospect of circumventing the traditional method or at least minimizing its use is very attractive. Rapidly identifying qualified, interested investigators who clearly have an unmet need is a true value added service for the bio-pharmaceutical industry, who experience delays in more than 90 per cent of their trials due to lengthy budget negotiations, slow IRB approval and poor patient recruitment. Companies know that motivated investigators are highly accountable when it comes to meeting important milestones such as obtaining ethics committee approval, and entering a first patient on study. These investigators are also highly likely to respect their patient enrolment target. The commitment and responsiveness they show has a favourable impact on both the quality and the cost of conducting a trial. Furthermore, when companies use the “Reverse Feasibility Program” in Canada, they have access to the expertise in oncology clinical trials and the privileged business relationships that the Scimega team has developed over the past 12 years.

For Canadian investigators, being part of the program means they reduce time spent reviewing information related to clinical trials that do not represent an opportunity for their site. This valuable time may then be redirected to other issues requiring their attention. The Reverse Feasibility™ Program is not a panacea for all the challenges that exist in the complex world of oncology clinical drug development. However, the approach brings together Canadian oncology clinical research professionals in an attempt to positively impact areas of high priority to clinicians and industry, such as advancing quality clinical research and containing costs through greater efficiency and quality.

References
1. Canadian Cancer Society – Canadian Cancer Statistics 2009
2. Health Affairs – Volume 25, number 2 page 420-423 (March-April 2006)

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