Oncology – A Bouquet of Rare and Ultra-rare Diseases

Oncology clinical trials are widely recognised as being amongst the most complex trials to design, set up, and deliver. Whilst there is good progress in finding optimal and durable treatment solutions for several cancer indications, the implementation of the enhanced understanding of molecular pathology adds an additional layer to clinical trial operational complexity, and makes finding increasingly discrete subsets of patients increasingly difficult. The demand to find treatment responses for various cancer indications is high, the research is intensive, and the number of sophisticated clinical trials is great. It is a major challenge for those working in clinical operations to succeed in timely delivery of the trials; to achieve this creativity is more needed than ever before.

Modern molecular biology supports the hypothesis that cancer is actually hundreds or thousands of rare diseases. Several different clones of tumour cells grow simultaneously in each tumour and every patient's cancer is, to some extent, unique.[1] This partly explains why large-scale randomised clinical trials that test drugs individually in heterogeneous populations are often inefficient and bring disappointing results. Oncology trials nowadays are becoming highly specific by defining the targeted patient population using genetic markers of the studied malignancy that leads the main inclusion criterion to become a 'rare-' or 'ultra-rare' disease; hence, oncology studies can't be run without the novel operational techniques utilised in rare-diseases trials.

As an example, the age-standardised rate per 100,000 humans of lung cancer is about 42, and non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers.[2] Recently, molecularly targeted therapies have shown remarkable benefit in NSCLC patients with specific genetic alterations. In particular, NSCLC with mutation in the epidermal growth factor receptor (EGFR) gene are sensitive to EGFR blockade with specific tyrosine kinase inhibitors (TKIs). Depending on the patient's ethnicity, the EGFR mutation frequency is between 17 per cent (Caucasians) and 47 per cent (Asians) of all NSCLC cases.[3] In spite of demonstrable efficacy, almost all patients with EGFR-mutant NSCLC develop resistance to EGFR-TKIs within 12 months and require further therapy. Various mechanisms of resistance to EGFR-TKIs have been identified, and understanding these is critical for development of effective treatment strategies for EGFR-TKI-resistant NSCLC. The major mechanism of acquired resistance reported is secondary T790M mutation on the EGFR gene, and additional mechanisms include amplification of the MET gene, PIK3CA mutation, BRAF mutation, epithelial-to-mesenchymal transition (EMT), and small cell lung cancer (SCLC) transformation. Each of these mechanisms requires different treatment strategies that can only be developed by working in these niche settings: the ASR for T790M mutated EGFR positive NSCLC patients is between 1-3 cases per 100,000, right at the mark for 'ultra-rare disease' definition of 2 in 100,000.

To successfully run oncology trials, pharma companies or CROs must use the complete arsenal of operational methods of classical oncology trials together with those used in 'rare diseases' indications, combined with novel operational and design strategies that are reshaping the drug development paradigms towards a truly patient-centric approach.

Collaboration with large oncology institutions remains essential; these sites are often specialised to treat broad cancer indications, are skilled in complex screening procedures, and are educated in running clinical trials. Beyond the highly specialised therapeutic qualification of the participating centres, 'rare disease trial' features dominate the operational conduct of the oncology trials. Their planning and execution has more in common across distant indications that are similarly rare, than with other indications in the same therapeutic area. Even with the involvement of the most prestigious centres, finding suitable patients for a given trial as defined by the genetic markers is akin to finding a *needle in a haystack*, a hard task that requires a highly innovative approach and close collaboration of parties. It is common to see large sites only enrolling one or a few patients in a year, or even not succeeding to enroll patients at all. The high number of screen failures is a waste of time and resources for developers and sites, as well as a disappointment for heavily diseased patients. A number of operational, technical, and trial design responses to these challenges are outlined below.

The need to find sufficient numbers of patients with a specific biomarker has generated large co-operative study groups. Consortia provide multiple molecular testing assays for patients and help them find the trial that is appropriate to their disease. An example of such large cross-sector initiatives is the government-based National Cancer Institute – Molecular Analysis for Treatment of Choice (NCI-MATCH). Cancer-specific advocacy groups can also lead co-operative study groups, such as the "Know Your Tumor" programme, established by the Pancreatic Cancer Action Network in the USA. The competition between oncology drug developers to partner with consortia is understandably ferocious.

Another patient-centric approach is to "bring the site to the patient" as opposed to the traditional way of attracting the patients to initiated sites. In these cases, the sites are only activated when a suitable patient has been pre-identified for the trial. This is a scalable solution that can work well; however activating a centre for drug release might require some time, and cancer patients can't be made to wait long to get their treatment.

A specific response of the oncology community to the poor operational efficiency because of the fragmented cancer indications is given by the use of novel clinical trial designs. One way is **the umbrella trial**, which uses different drugs on different mutations in a single type of cancer ('under the umbrella of one disease'). Patients are selected based on the genetic mutation most prominent in their tumour and treated with a number of medicines known to target this specific mutation. This approach helps researchers to confirm patient subgroups who would most benefit from those medicines tested. INC Research is involved in running the large umbrella trial called "Beat AML" for acute myeloid leukaemia patients.

Basket trials test the effect of a drug on a specific mutation in a variety of cancer types ('baskets'), allowing researchers to gain more

information about each individual cancer type, as well as assess the impact of the drug as a whole. The results of the first successfully run basket trial were published in 2015[4] and there are numerous such trials ongoing at the moment. Using this approach, it is possible to complete multiple Phase II trials through a single study, thus greatly speeding up the development process and expediting the delivery of an effective treatment to the patient.

Conclusion

Recent discoveries made in the molecular pathology of cancer diseases are creating opportunities for developing therapies with durable clinical benefits, while challenging the existing drug development process paradigms. Succeeding in the world of oncology clinical trials is becoming increasingly difficult for drug developers, who don't only need to find the best drug candidate, but also need to find the responses to the operational difficulties caused by narrow indications, and the highly competitive and extremely agglomerated clinical trial landscape. In addition to the therapeutic expertise, clinical operations experience from 'rare diseases' trials and other areas are equally important for the developers to serve as a basis for creative solutions to these challenges. By generating a truly patient-centric mindset, the novel design and operational solutions in place in modern oncology represent important successful early steps towards precision medicine.

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Jozsef Palatka

MD, Vice President of Clinical Development of Oncology, INC Research, has 17 years of clinical research and drug development experience gained from working as Drug Design & Development Lead, as well as in various roles in project management and global trial clinical operations of oncology studies. Dr Palatka holds a Doctor of Medicine degree from Semmelweis University of Medicine in Budapest, as well as a Masters' of Science in Biomedical Engineering from University of Technical Sciences in Budapest.

E-mail: jozsef.palatka@increasearch.com