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THE ROLE OF PHARMACOVIGILANCE IN ONCOLOGY DRUG TRIALS

Investment into oncology drugs has displayed an upward trend across the last decade, with Statista predicting revenue in this market will increase at a Compound Annual Growth Rate (CAGR) of 13.8% between 2024 and 2028.

Multiple factors have contributed to this growth. The global burden of cancer is rising, for one, and we're seeing an increasing number of cancer diagnoses each year, reflecting both an ageing population and improved diagnostic techniques. In the UK, a 2023 report by Cancer Research found cancer cases are expected to increase from 384,000 to over half a million by 2040. Figures show a similar pattern in the United States, where the National Cancer Institute says annual cancer cases are projected to rise to approximately 2.3 million by 2040 (up from 1.9 million in 2023).

Secondly, advancements in biotechnology and precision medicine are transforming the oncology field, leading to more targeted therapies and effective cancer treatments. These treatments are attracting significant investment from both the public and private sectors, with pharmaceutical companies increasingly prioritising oncology in their research and drug development pipelines.

However, as medical advancements revolutionise cancer research and therapies, safety control is a crucial consideration. With new treatments being developed at a rapid pace, monitoring drug safety is essential to identify and manage risk – ensuring the immediate and long-term safety of emerging therapies.

The aim of pharmacovigilance (PV) is, first and foremost, to ensure the safety and well-being of patients by detecting, assessing and preventing potential Adverse Drug Reactions (ADRs).

Cancer treatments are often aggressive; chemotherapy, immunotherapy and targeted therapies come with a whole host of possible side effects, ranging from mild to life-threatening. Equally, the margin between therapeutic and toxic doses can be narrow in oncology – with individual responses to treatment varying drastically.

Given the complexities and high stakes involved in cancer treatments, including the high toxicity level and relatively low cure rate of current treatments, vigilant monitoring of ADRs and continued research into treatment options is essential to ensure patient safety and optimise treatment efficacy.

Maintaining stringent quality control measures to mitigate the risks associated with cancer therapies only becomes more imperative as the pipeline of new oncology drugs continues to grow. For instance, advances in genomics and biomarker research have enabled the development of more targeted immunotherapy treatments, such as CAR T-cell therapy, through genetic engineering.

CAR T-cell therapy is a complex and specialist treatment that involves extracting T-cells, a type of white blood cell, from the patient's blood and changing them into CAR (Chimeric Antigen Receptor) T-cells in a laboratory before adding them back into the patient's bloodstream. These CAR T-cells are designed to recognise and target a specific protein in the cancer cells.

Changing these cells in the lab means they can stay in the body for longer periods of time, continuing to attack specific cancer cells. However, research into how long these cells might stay in the body is ongoing, which poses the question: what are the potential long-term side effects?

This issue is not unique to CAR T-cell therapy. Advanced cancer treatments often involve intricate biological interactions and compounds, as well as complex mechanisms of action, which can lead to unpredictable side effects and long-term health implications.

Pharmacovigilance is, therefore, pivotal within oncology drug trials, from early-stage clinical trials through to post-marketing.

With real-time data collection and ongoing monitoring of drug safety, PV enables the timely identification and management of ADRs, allowing for the early detection of potential risks, that may not have been apparent during clinical trials, to continue building the safety profile of both existing and emerging treatments.

Maintaining and updating pharmacovigilance best practices is, therefore, essential to the future of cancer research – especially for rarer forms of the disease. But what challenges are sponsors and the Clinical Research Organisations (CROs) that work on behalf of them facing in this area?

'Pharmacovigilance is, therefore, pivotal within oncology drug trials, from early-stage clinical trials through to post-marketing.'

THE CHALLENGES OF PV IN ONCOLOGY

During trials, there are a number of multifaceted pharmacovigilance challenges and this is especially the case in the rapidly evolving field of oncology.

DISEASE COMPLEXITIES

Many of the challenges associated with pharmacovigilance in oncology stem from the intricacies of cancer itself, as well as the therapies used to treat it.

Cancer is a broad term used to describe a heterogeneous group of diseases that may occur in any body system. The causes and risk factors vary between cancers, as do their effects on the body. Thus, the methods used to treat them must be suitably varied and tailored to the specific type of cancer.

Oncology therapies often involve a combination of traditional chemotherapy, targeted therapies and immunotherapies – each with distinct mechanisms of action and side-effect profiles. So, when you talk about the role of pharmacovigilance in oncology drug trials, you have to consider two components: not only the natural history and the evolution of the disease, but also the toxicity of current treatments.

When bringing in new treatments with unknown safety profiles, you must be able to identify what is responsible for each part of a specific adverse event. Is this event, likely related to the natural history of the disease or comorbidities, to the drugs the patient is using or to the new therapy regimen being superimposed? The answers to these questions aren't always clear, so this is a key role of PV in the oncology environment.

Platform trials (which are designed to evaluate multiple treatments simultaneously within a single overarching trial structure) are also becoming increasingly popular in oncology. In these larger studies, the interactions and the way you handle pharmacovigilance are much more complex and require integration on a completely different scale.

In rare cancers – such as ocular melanoma or Cutaneous T-Cell Lymphoma (CTCL) – these challenges become more complicated. With rare diseases, we have even less knowledge of what is expected for the condition and few clinical trials or drugs have been tested specifically for that indication. Cancer patients with rare forms of the disease often receive treatments tested in other indications that, based on the mechanism of action and type of cancer, are expected to be efficacious. Yet, because this drug wasn't tested on this particular group of patients (or tested in a very small set of people), we might see side effects reported that weren't seen during the original clinical development programme – adding another layer of safety concern.

Likewise, advancements in drug efficacy are resulting in many cancer patients living longer than before. The prognosis for children with Acute Lymphoblastic Leukaemia (ALL), for instance, has improved significantly over the past few decades due to treatment innovations, with the overall five-year survival rate for children with ALL now sitting at around 90%. Whilst positive, these developments create a degree of uncertainty and knowledge gaps within pharmacovigilance. How do you know what long-term effects the treatment will have – on reproductive status, for example – if the patients have previously never lived long enough for these effects to be considered?

Signal detection, therefore, becomes increasingly important when working with low case numbers or in reduced knowledge environments. Not only is it crucial to understand as much as possible about that particular type of cancer, but the pharmacovigilance team supporting the product must also shift their mindset to maintain a high suspicion level to build a detailed side-effect profile.

SOURCING DATA

The sheer volume and variety of data sources – including clinical trial data, electronic health records, patient registries and real-world evidence – can also be overwhelming. Then there's the matter of the quality of the information.

There are certain adverse reactions that, even if they occur only once, will raise significant concern. But what about the other reactions that build over time? This is where signal detection is vital in both clinical development and post-marketing to glean understanding from possibly a larger number and variety of adverse event reports.

However, during post-marketing authorisation case processing, there's often limited scope to approach people to get that information and the amount of information you may receive is typically quite small. In a clinical trial situation, where you have direct contact with the investigator who is following the patient regularly and collecting this data, you may be able to gather much more evidence. But in post-marketing, the person making the report is often the patient, a family member or a caregiver – you may not have access even to the physician who is seeing that patient. So, the quality of the data is usually more superficial and far less accurate than in a clinical trial setting, compromising the overall capability of signal detection.

Yet, you are duty-bound as a CRO or as a pharmaceutical company to gather more information, discerning the trends to help understand whether there's cause for concern and then modify how that drug is used going forward. As such, it's important to have robust data management systems and processes to collect, integrate and analyse this information effectively.

POST-MARKETING VARIABLES

The post-marketing phase is arguably the most challenging for pharmacovigilance.

Real-world insights can help to highlight potential safety concerns and, ultimately, bring safer cancer treatments to market. However, gathering this data presents several issues due to the high number of variables and lack of control in real-life situations.

In a clinical trial situation, you'll have a clear profile and know every patient is going to follow a similar path as you'll be testing a drug with perhaps one or two other interventions and set controls in place. When the drug is used in the real world, you lose this control. So, it's crucial to consistently monitor how a drug is being used by patients and combined into therapy to interpret and understand the safety profile of the drug. Plus, as we stated earlier, oncology drugs are not necessarily used to the indication they were tested in when it comes to post-marketing. Patients with rare forms of cancer often also receive off-label treatments.

Then there's the matter of geographical, socioeconomic and epidemiologic disparities to contend with.

Once a drug is in the post-marketing phase, you're potentially looking at more and more interactions and dealing with an increasing number of people from different backgrounds and different starting points in their treatment, as well as different healthcare systems. All these confounding factors must be considered when managing a product's PV activities.

As such, it's crucial to record what's happening but also who it's happening to. Are the adverse events more common in females than males? Are they typically younger or older? Are there any correlations between race, ethnicity, co-morbidities, habits (e.g. tobacco smoking) or other medications?

Local practices and regulations can also play a part here. For example, if Drug A is approved in one region but not another, it's reasonable to assume the number of adverse events from other drugs may be disproportionately higher in the regions where Drug A is not approved if there are fewer alternative treatment options available.

However, when analysing this kind of data, we have to look at the estimated drug exposure in the specific period (number of cases per exposed population) not just the number of cases per population. Understanding the geographical particularities, therefore, helps to plan and interpret the obtained data.

From a pharmacovigilance viewpoint, this means constantly monitoring ADRs to understand why they have occurred – taking medical, geographical, socioeconomic and epidemiologic disparities into consideration – and expressing findings clearly to build a comprehensive overall safety profile of treatments.

BEST PRACTICES FOR PV IN ONCOLOGY

Pharmacovigilance best practices are essential for the future of cancer research and clinical trials. Maintaining compliance with and adapting to changing regulatory requirements, such as the FDA's updated guidance around secondary malignancies and CAR T-cell therapies, is perhaps one of the more obvious best practices to adhere to. But as the landscape of oncology evolves with emerging therapies, it's imperative that we also enhance pharmacovigilance frameworks to address the unique challenges posed by cancers – particularly rarer forms of the disease.

As we've discussed, the rarity of certain cancers means clinical trials generally have small patient populations and patients often receive off-label treatments – limiting and further complicating the collection and analysis of data. To address these challenges, PV best practices must be updated to include more comprehensive data collection methods and foster patient engagement, leveraging advanced technologies such as Artificial Intelligence (AI) and Machine Learning (ML) whilst also focusing on training and collaborative networks.

ADVANCES IN TECHNOLOGY

In the past, PV relied heavily on spontaneous reporting systems and manual data analysis, which often resulted in underreporting and delays in signal detection. However, the field has evolved significantly in recent years thanks to the integration of electronic health records and the establishment of large-scale pharmacovigilance databases, such as the FDA's Adverse Event Reporting System (FAERS). Now, the integration of innovative technologies such as AI and ML are transforming pharmacovigilance processes, holding great promise for enhancing quality control in oncology.

AI and ML algorithms can analyse large datasets from various sources – including clinical trials, real-world evidence, electronic health records and patient-reported outcomes – to detect and predict patterns of ADRs, thus improving the speed and accuracy of safety assessments. Natural language processing tools can even analyse unstructured data, such as clinician notes and patient narratives, to extract relevant safety information. This expands the scope of pharmacovigilance to include valuable insights not captured in typical structured data formats. By integrating AI and ML into pharmacovigilance systems, CROs and healthcare providers can also predict which patients are most likely to experience adverse effects based on their genetic profiles, comorbidities and treatment histories.

From a patient perspective, AI and ML can also be incredibly useful. For example, wearable devices and mobile health apps can collect real-time data on vital signs and medication adherence, enabling continuous monitoring of patients and symptom reporting. This data can then be integrated into pharmacovigilance systems, upon consent, to provide a more dynamic view of drug safety.

These digital tools empower patients to report ADRs directly and provide feedback on their treatment experiences, enhancing patient engagement in the pharmacovigilance process. Patients, particularly those with rare cancers, often have valuable insights into the real-world impacts of their treatments, which can complement clinical data. As such, it's vital to establish robust channels for patient-reported outcomes and ensure patients' perspectives are considered to enhance the quality of safety data in both clinical trials and post-marketing settings.

ENHANCED TRAINING AND COLLABORATION

Investment in training clinical teams, from research nurses and clinicians to investigators, should also be a priority in pharmacovigilance trials, particularly in oncology. Indeed, unless you have experienced drug developers and safety reviewers evaluating the relevant data during drug development, a compound may be prematurely deemed a 'failure', thus preventing a potentially lifesaving or quality-of-life-enhancing product from ever reaching the patients in need.

Trials for cancer drugs are often held at specialist sites where patients are being treated, meaning the trials can quickly become somewhat of a burden. Clinicians are busy looking after patients, and even if there is a dedicated research nurse, they may have other trials running simultaneously.

> 'Bringing new drugs to market is a balance between safety and efficacy, especially in the case of rare life-limiting cancers.'

Equally, patients often don't want to deal with the intricate questions of severe adverse events forms and it can be difficult for clinical teams to know exactly what PV teams want from the data. As such, the quality of the data can be negatively impacted.

So, it's important to ensure sufficient training is in place and build bridges with the individual sites. Having someone from pharmacovigilance involved from the outset of a trial helps ensure the clinical team complies with all relevant regulations and supports them in gathering the information needed for evaluations.

However, the principal best practice to take forward in pharmacovigilance is collaboration between CROs, pharmaceutical companies, healthcare providers, regulatory bodies and patient advocacy groups.

Bringing new drugs to market is a balance between safety and efficacy, especially in the case of rare life-limiting cancers. Although a treatment may have serious side effects, if it's prolonging the life of patients who would otherwise have had no treatment options, how does the efficacy stand up against the risks?

PV predominantly looks to build a real-time safety profile, which will influence effective risk management plans. Of course, pharmacovigilance teams do consider the number of patients and whether, in fact, that is suggestive of the risk-benefit when preparing development safety update reports. But generally, they aren't analysing clinical trials to determine if the risk-benefit is good or bad, they're looking at the side effects.

This is where collaboration and the appropriate sharing of information (for example, via safety data exchange agreements) are crucial, particularly in post-marketing when reporting is more periodic. PV systems must, therefore, be agile enough to produce ad-hoc reports and communications with relevant bodies – offering insights from all areas to help make sense of the research and contribute meaningfully to the risk-benefit discussion.

CONCLUSION

As cancer therapies continue to evolve, the role of pharmacovigilance will become even more critical, ensuring the advancements in cancer treatments translate into real-world benefits for patients whilst minimising risks.

The sheer volume and variety of data sources, coupled with the complexities of the disease and its therapies, demand robust data management systems and advanced signal detection methodologies. Ensuring accurate and comprehensive data collection is, therefore, critical – especially in post-marketing when dealing with real-world variables and adverse reactions that may not be immediately apparent.

However, whilst the compounds in development and the systems used for processing clinical trial and safety data are getting ever more complex, the analysis of risk-benefit and, in particular, the concept of acceptable risk still depends on people and experience.

Collecting the data from different sources is only half the battle. Continuously analysing and interpreting the data during the development and commercialisation phases of the drug life cycle, and turning this data into something meaningful, is what makes the greatest difference within PV and oncology. Only this continuous activity linked with sophisticated tools like AI and ML will result in better decisions and more information being available to produce better outcomes for cancer patients, regardless of the rarity of their condition.

PROFILES

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