Integration of Cardiac Endpoints

Within R&D and drug development, there is growing insight and direction related to the integration of ECG and blood pressure, as well as cardiac imaging endpoints in oncology clinic trials

Jeff Heilbraun at Bioclinica

Within the pharmaceutical R&D arena, there is continued growth in the field of oncology research. As with any other field, efficacy is a primary goal and endpoint for developing oncologic agents. Based on the therapeutic area, the approach to safety endpoints is defined through a benefit-risk perspective. The success in the field of oncology research has been significant and patient's life expectancy following treatment continues to improve with advanced therapeutic approaches. It has been well recognised that many of the oncology therapeutic treatments are cardiotoxic in nature. This was captured back in 2010 by Albini *et al*, stating "cardiotoxicity is becoming one of the most important complications of cancer chemotherapy and, sometimes, of cancer chemoprevention. Identification of those patients at higher risk will be one key strategy to reduce the morbidity and mortality from cardiotoxicity" (1).
With the recognition that some treatments had a cardiac safety profile and patients were in fact living longer, the medical and scientific community began to focus on the cardiac safety considerations, and a new specialty arose that incorporated both the cardiovascular safety endpoints as well as the treatment of the cancer, leading to the establishment of the field of cardio-oncology.

From a clinical care, drug development, and regulatory perspective, there is continued momentum in this focus and specialty, which can be seen coming from the American College of Cardiology (cardio-oncology roundtable and development of the online cardio-oncology community) to the American Heart Association's (AHA) Cardio-Oncology Vascular and Metabolic Perspectives scientific position paper (2). This has also been mirrored in the pharma R&D groups with the integration of a cardiologist within the oncology development team and with the specific therapeutic reference to cardio-oncology. Additionally, working groups such as the Cardiac Safety Research Consortium (CSRC), which includes representation from the regulatory, pharma, and clinical arenas, have conducted think tanks related to cardiac safety and oncology drug development (3).

Discussing cardiac safety and oncology drug development often includes the following diagnostic measures around electrocardiography (ECG), hemodynamics (blood pressure [BP]), cardiac function (cardiac imaging), and biomarkers (blood/serum sample analysis). It is important to review the present regulatory considerations as well as the technologies and modalities used for the assessment of cardiac safety and imaging endpoints within a study from a benefit-challenge perspective, and how the design and data are positioned to address specific safety endpoints within the unique oncology drug development environment.

Cardiac Safety: QT Assessment

From a cardiac safety perspective, the ECG (QTc) is the most recognised regulatory endpoint related to drug and biopharma development. The approach to addressing the risk of sudden death and/or torsades de pointes associated with an non-antiarrhythmic compound related to QT prolongation is outlined in the ICH-E14, along with a series of questions and answers as there have been some considerations to the guidance. Additionally, the field of assessing cardiac safety in drug development continues to evolve based on scientific progress. The thorough QT (TQT) had been the primary trial to address the QT cardiac safety of a developing compound. This dedicated study often includes a placebo arm, a therapeutic treatment arm, a supratherapeutic treatment arm, and a positive control arm with healthy volunteers as study participants. The approach to this dedicated study has expanded to include additional trial designs, but for developing oncologic agents, it still provided a unique challenge. It is clear that conducting oncology studies in healthy volunteers may not be feasible for many compounds

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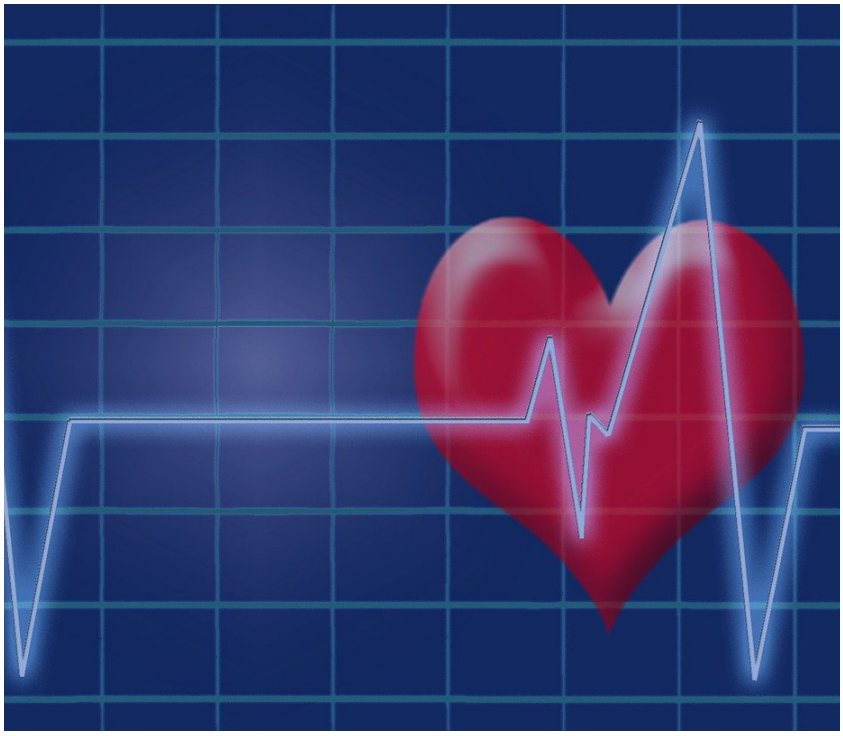

based on cardiotoxicity, and implementation of a placebo arm or supratherapeutic dose in an oncology patient population would not be an appropriate design option. Regarding oncology drug development, the FDA has provided some direction and is also referenced in the ICH-E14 R3 questions and anwers with a special consideration section. The FDA position is, "In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the 'TQT' study may be appropriate. Please plan to address this issue early in development". The FDA now requests QT data for oncology products that cannot be tested in a TQT study, using alternative approaches. Approve oncology compound labels do reference warnings regarding cardiac repolarisation (QTc).

An article in 2008 by Serapa and Britto provides a review of the challenges of implementing the ICH-E14 guidance in oncology studies and proposes an integrated approach to QTc risk assessment (4). The alternative QTc study in oncology drug development looks to maintain aspects of the traditional TQT, but eliminates components that cannot be ethically implemented based on the therapeutic indication and population. Within oncology trials, it is important to remember that even the early trials are focused on disease control. There is more of a focus on exposure response modelling with implementation in early phase single ascending dose/multiple ascending dose studies. These studies will have more intensive ECG collection around the PK sample collection, similar in nature to ECG/PK timepoint collection in a formal TQT or IQT study. In a recent publication, Mendzelevski *et al* provide a good example of approaching QTc trials within oncology drug development (5).

Cardiac Safety: Blood Pressure

For specific oncology therapeutic agents, there is a well-recognised BP response (increase) associated with the treatment. Many of the vascular endothelial growth factor (VEGF) inhibitors generate an increase in an oncology patient's BP. From a clinical management perspective, the Maitland *et al* publication in 2010 for the National Cancer Institute task force provides a good guideline for identifying and managing the BP risk, which included (6):

- Conducting and documenting a formal risk assessment for potential cardiovascular complications
- Recognising that preexisting hypertension will be common in cancer patients and should be identified and addressed before initiation of VEGF signaling pathway inhibitor therapy
- Actively monitoring BP throughout treatment with more frequent assessments during the first cycle
- Managing BP with a goal of less than 140/90mmHg for most patients (and to lower, prespecified goals in patients with specific preexisting cardiovascular risk factors)

From a clinical trials perspective, implementing BP monitoring to identify a signal and response can be completed using a number of methodologies. A primary tool for this assessment is the ambulatory BP monitor (ABPM). This modality has several benefits, including capturing a 24-hour BP profile that provides the complete circadian rhythm. This allows for a dose response profile as well and the ability to compare the 24-hour response across different cycles/exposure to a baseline profile. A good example of the implementation of ABPM to define a BP signal was presented by Fishman *et al* in a poster at the 2010 ESMO meeting in Milan: "Axitinib pharmacokinetics and blood pressure changes in frontline metastatic renal cell carcinoma patients". By implementing ABP monitoring into the study, they were able to conclude that:

- Axitinib-induced increases in dBP and sBP occurred early, by day four of treatment, and remained consistent two weeks after initiation of axitinib therapy, supporting early monitoring and management of BP
- The observed BP responses appeared to be independent of axitinib plasma exposure

In addition to ABPM, BP can be monitored in clinical trials using automated office BP units as well as using remote or standard automated home BP monitors.

Cardiac Safety: Cardiovascular Imaging

During the ACC Advancing the Cardiovascular Care of the Oncology Patient, held on 14-16 February 2020 in Washington DC, US, Dr Dinesh Thavendiranathan presented a session titled 'Cardio Imaging 101: When, Which Test; Why and How?' Although his presentation had a clinical management focus, it was applicable to consideration for clinical trials. Regarding why to conduct cardiac imaging: to identify cardiac disease and to risk stratify by assessing prior to treatment, during treatment, and post treatment. The other key point was to prevent prognostically important cardiovascular diseases and avoid unnecessary interruption of cancer therapy (7). There are a number of cardiovascular imaging modalities that are being implemented in oncology clinical trials. Primary approaches include standard echocardiography, strain echocardiography, and cardiac magnetic resonance. Which modality selected depends on the cardiac function and/or cardiac disease state that is the focused endpoint.

From the oncology drug development and clinical trials perspective, there is growing recognition of the benefit and importance of working with a centralised cardiovascular imaging core lab. The CSRC paper summarised the primary benefits well, "The CV imaging core laboratory role is to ensure robust and consistent data collection. This includes involvement with protocol development and definition of CV endpoints… Independent, centralized and standardized analysis and quality control" (3).

Summary

There is a clear benefit for both oncology clinical management and oncology drug development to embrace the growth of the cardio-oncology initiative. The oncology therapeutic indication is unique from a drug development perspective with a focus on the benefit-risk profile of new therapeutic agents. Although a treatment may present a cardiac safety signal, whether through ECG, BP, or cardiac imaging, that does not mean it should stop in development. The goal is to identify the potential safety signal using the appropriate trial design, endpoints, and modalities to support both regulatory requirements and clinical management within the oncology therapeutic indication. The AHA scientific statement provided a number of future research directions in cardio-oncology, and one of the top directions was "more rigorous identification of cardiovascular and cardiometabolic side effects during clinical trials and in real-world populations after drug approval" (2). This is the path we should continue to follow. An additional interesting future direction was to implement cardiovascular adjudication within oncology clinical trials, which is becoming more important from a cardio-oncology perspective in drug development.

References

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Jeffrey Heilbraun attended the American University in Washington DC, US, receiving a fellowship and completing his Masters of Science in Health Promotion and Disease Management. Jeffrey completed his Bachelors of Science in Biology at Tufts University, US. He joined **Bioclinica** in 1993 and has supported activities in data management, operations, and business development. Jeffrey has presented and chaired sessions at the Annual DIA meeting, The Japan DIA Cardiac Safety Meeting, and CSRC. He has also been involved in the biopharma cardiac safety arena for 25-plus years and worked on the publication of several articles specific to the area of cardiac safety in pharma development.