Ongoing research developments in cardio-oncology


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Dr. Susan Dent and **dr. Daniel Lenihan** moderated session 5 highlighting ongoing research in cardio-oncology. Topics discussed included: acceleration of new drug approval, new strategies for drug safety and efficacy assessment, and interactions between different pathways of cellular metabolism. **Dr. Laleh Amiri-Kordestani** (Centre for Drug Evaluation and Research, FDA) spoke on accelerated FDA approval for oncology products: „Is there a different safety bar?". Dr. Amiri-Kordestani emphasized the very low success rate of drug discovery in oncology. Only 5 of 5000 potential oncology compounds will move from pre-clinical studies to phase I clinical trials. On average drugs in oncology require 3–6 years of pre-clinical research and 6–7 years of clinical trials before approval. In order to expedite the approval of effective and safe drugs, the FDA has developed 4 expedited programs: Fast Track Designation, Priority Review Designation, Breakthrough Therapy Designation, and Accelerated Approval Pathway.

Efficacy endpoints for regular FDA approval are usually based on direct measures such as improvement in overall survival ("prolongation of life"), or established surrogates such as improvement in quality of life ("a better life"), or disease-free survival (DFS). Accelerated approval is usually based on the demonstration of a meaningful advantage over available therapies (superiority design) for serious or life-threatening conditions (oncology), or usage of a surrogate or intermediate endpoint reasonably likely to predict clinical benefit (smaller, quicker trials) [1]. Drugs which receive accelerated approval are often subject to further studies (post-marketing trials) to verify efficacy and safety [2]. The accelerated approval approach adopted by the FDA permits more rapid access of potentially life-saving therapies, including cancer treatments, while ensuring the safety and protection of the public from potential harm [1, 2].

Dr. Todd Palmby (Supervisory Pharmacologist, Food and Drug Administration, Washington, DC) discussed "New developments of cardiac safety with oncology therapies: FDA perspectives".

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Drug development is currently based on the principles of ICH S9 Guidance: Nonclinical Evaluation for Anticancer Pharmaceuticals: "This guidance aims to facilitate and accelerate the development of anticancer pharmaceuticals and to protect patients from unnecessary adverse effects…" [3].

Nonclinical Toxicology studies have been less predictive of human toxicities for small molecule targeted anticancer drugs, such as the tyrosine kinase inhibitors, compared to traditional cytotoxic drugs [4]. If clinical adverse reactions are not predicted prior to phase 1, appropriate monitoring and clinical trial design may miss clinically relevant dose limiting toxicities (including cardiotoxicity) prior to entering a phase 2/3 trial. This is problematic if dose selection is based on a maximum tolerated dose from the phase 1 trial. The unique toxicities associated with targeted therapies may emerge after many weeks/months of dosing thus highlighting the need to modify surveillance strategies [5]. The assessment of cardiovascular toxicity in clinical trials has generally been poorly conducted. The prospective evaluation of cardiovascular toxicities should be incorporated into future trials evaluating all novel therapies, including targeted cancer agents. "Because malignant tumors are life-threatening, the death rate from these diseases is high, and existing therapies have limited effectiveness; it is desirable to provide new, effective anticancer drugs to patients more expeditiously".

Dr. Kathleen Gabrielson discussed the "Bidirectional cross-regulation between ErbB2 and β-adrenergic signaling pathways". This animal-based work studied bidirectional cross-regulation between ErbB2 and β-adrenergic signaling pathways and the relationship between ErbB2 and β1- and β2-adrenergic receptors [6]. His data supports our current understanding of the role for β-blockers in anthracycline and anti-ErbB2 cardiotoxicity prevention [6]. Chronic treatment of mice with isoproterenol, with or without ErbB2 kinase inhibition, shows that ErbB2 is protective and important in its transactivation role in the heart although future evidence-based data is required.

This session concluded by highlighting the need for ongoing research in cardio-oncology. Prospective clinical research will help define optimal strategies for the prevention and early detection of cardiotoxicity as well as, treatment of cancer therapy--related cardiotoxicity.

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References

1. Amiri-Kordestani L, Beaver JA, Cortazar P. Neoadjuvant Therapy As a Platform for Drug Development: Current Controversies and Regulatory Perspectives. Oncology (Williston Park) 2015; 29(11): 843-844, 846.
2. Amiri-Kordestani L, Wedam S, Zhang L et al. First FDA approval of neoadjuvant therapy for breast cancer: pertuzumab for the treatment of patients with HER2-positive breast cancer. Clin Cancer Res 2014; 20(21): 5359-5364.
3. International Conference on Harmonisation; Guidance on S9 Nonclincal Evaluation for Anticancer Pharmaceuticals; availability. Notice. Fed Requist 2010; 75(44): 10487-10488.
4. Dy GK, Adjei AA. Understanding, recognizing, and managing toxicities of targeted anticancer therapies. CA Cancer J Clin 2013; 63(4): 249-279.
5. Herndon TM, Deisseroth A, Kaminskas E et al. U.S. Food and Drug Administration approval: carfilzomib for the treatment of multiple myeloma. Clin Cancer Res 2013; 19(17): 4559-4563.
6. Sysa-Shah P, Tocchetti CG, Gupta M et al. Bidirectional cross-regulation between ErbB2 and β-adrenergic signalling pathways. Cardiovasc Res 2015; Dec 21. pii: cvv274 [epub ahead of print].