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Workshop report

HESI/FDA workshop on immunomodulators and cancer risk assessment: Building blocks for a weight-of-evidence approach

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ABSTRACT

Profound immunosuppression (e.g., AIDS, transplant therapy) is epidemiologically associated with an increased cancer risk, and often with oncogenic viruses. It is currently unclear how broadly this association translates to therapeutics that modulate immunity. A workshop co-sponsored by the FDA and HESI examined how perturbing the immune system may contribute to carcinogenesis, and highlighted priorities for improving non-clinical risk assessment of targeted immunomodulatory therapies. Conclusions from the workshop were as follows. 1) While profound altered immunity can promote tumorigenesis, not all components of the immune system are equally important in defense against or promotion of cancer and a similar cancer risk for all immunomodulatory molecules should not be assumed. 2) Rodent carcinogenicity studies have limitations and are generally not reliable predictors of cancer risk associated with immunosuppression. 3) Cancer risk needs to be evaluated based on mechanism-based weight-of-evidence, including data from immune function tests most relevant to tumor immunosurveillance or promotion. 4) Information from nonclinical experiments, clinical epidemiology and immunomodulatory therapeutics show that immunosurveillance involves a complex network of cells and mediators. To support a weight-of-evidence approach, an increased focus on understanding the quantitative relationship between changes in relevant immune function tests and cancer risk is needed.

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1. Introduction

Patients, physicians, regulatory authorities, and the pharmaceutical industry all struggle with the challenge of assessing the potential carcinogenic risks associated with the use of therapeutics

Abbreviations: CTL, cytotoxic T-lymphocytes; EBV, Epstein–Barr virus; FDA, Food and Drug Administration; HESI, Health and Environmental Sciences Institute; HIV/AIDS, Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome; HPV, human papilloma virus; ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; IFN, interferon; IL, interleukin; LCV, lymphocryptovirus; NK, natural killer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; T_H, helper T cell; TNF, tumor necrosis factor.

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that modulate immunity through varied and novel mechanisms (referred to as “immunomodulators” in this manuscript) and understanding their impact, if any, on tumor development and growth. This could lead to a decision to not utilize a potentially life-changing disease modifying agent due to concerns that the therapeutic could result in a future risk of cancer. A more complete understanding of the risks of a specific drug could better inform decisions regarding the choice of therapeutics for a given patient and could ultimately result in better disease management, enhanced monitoring for potential tumors, and increased ability to interpret the relevance of early reports of human tumors potentially associated with a specific therapeutic class of drugs or disease.

As limited long-term human data exist for a newly approved therapeutic, one of the objectives of the nonclinical development program is to characterize the carcinogenic risks of a product to inform the clinical use of the drug, and communicate risk to the prescriber and patient via product labeling. The carcinogenicity assessment for any therapeutic is particularly challenging for compounds that impact the function of the immune system. As a result of a lack of availability of relevant data to inform risk, drug product labels for immunomodulators frequently include the statement that the impact of the therapeutic on the development of tumors is not known, but that treatment with immunosuppressants may result in an increased risk for malignancies. While such a statement is notably based on the experience of transplant recipients who received immunosuppressive therapy to maintain an organ allograft, this may not be true for all immunomodulatory therapeutics, and better methods to characterize and assess carcinogenic risk for these compounds is clearly needed.

By international agreement, drug products intended for chronic or chronic-intermittent human use are required to be assessed for their carcinogenic potential prior to marketing application (ICH, 1995). For small molecules, this has traditionally been completed via either two life-time studies in rodents or via a single lifetime rat study and a 6-month transgenic mouse model (ICH, 1997). For biologic therapeutics, meaningful long-term studies in rodents are frequently not possible due to immunogenicity or lack of adequate cross-species pharmacodynamics (ICH, 2011). Nonetheless, a risk assessment for carcinogenicity potential for biologic therapeutics is still required. This assessment is generally based on a weight-of-evidence evaluation that takes into consideration the target biology and mechanism of action of the therapeutic, data from chronic toxicology studies, published information such as data from transgenic or knock-out animal models, human genetic diseases, and previous human experience with similar molecules. When this weight-of-evidence suggests a cause for concern, the potential hazard can be addressed by product labeling. When there are inadequate data to inform a product-specific assessment, additional mechanistically focused studies may be completed to better understand the risks of a therapeutic product.

Rodent lifetime carcinogenicity studies, which are commonly conducted to support small molecule clinical development and marketing applications, are used to help define the risk vs. benefit assessment and are summarized in product labeling information to communicate this assessment to physicians and patients. Such lifetime rodent studies have been able to detect many human genotoxic carcinogens, and to date, there is no better-characterized nonclinical model for risk assessment identified (Jacobs, 2006). In a survey of the literature, Bugelski et al. (2010) found that various rodent models, including 2-year carcinogenicity bioassays, are unreliable predictors of human cancer risk associated with immunosuppressive drugs (e.g, dexamethasone, prednisone, mycophenolate, methotrexate, tacrolimus, everolimus). These findings cast doubt on the predictive value of the 2-year carcinogenicity bioassay for immunosuppressive agents.

Given the clear challenge of assessing immunomodulatory compounds for cancer risk, the U.S. Food and Drug Administration (FDA) and the Health and Environmental Sciences (HESI) Immunotoxicology Technical Committee co-sponsored a public workshop in October of 2014 that was specifically intended to define points to consider when building a product-specific weight-of-evidence carcinogenicity assessment for either a small molecule or a biologic therapeutic affecting immunity. The workshop gathered together international leaders in the field of oncology, tumor development, and therapeutics from across industry, academia and government in an attempt to provide diverse insights into the mechanisms of tumor evolution and the impact of the immune system on this complex process. The workshop was broken down into four primary sessions to review the current knowledge on human cancer risk associated with altered immunity and the available models and tools to inform risk assessment. The ultimate objectives were to identify knowledge gaps to guide future research and to provide a framework to guide the development of product-specific weight-of-evidence carcinogenicity risk assessments for new immunomodulatory therapies. This manuscript presents highlights from the workshop, synthesizes the learnings of the organizing committee members into points to consider, and proposes a framework for how to conduct a weight-of-evidence based cancer risk assessment for immunomodulatory molecules.

2. Tumor necrosis factor (TNF) inhibitors and cancer risk

An introductory session was dedicated to TNF inhibitors (referred to as anti-TNFs, including TNF receptor fusion protein products), since experience with this class of marketed drugs illustrates how it has been challenging to evaluate and then communicate actual cancer risk for immunomodulators. In addition, the example of anti-TNFs is valuable given the plethora of information relative to the biology of the TNF pathway and the recent availability of human epidemiology data assessing the cancer risk associated with use of anti-TNFs. Overall, the data indicate that elevated TNF is a risk factor for cancer, whereas its inhibition is not generally associated with an increased cancer risk (Lebrec et al., 2015). Based on extensive clinical data for this class of drugs, targeted immunomodulation is not associated with the degree of cancer risk associated with profound immunosuppression or immunodeficiency.

The first anti-TNFs reached the market in 1998 (Remicade® [infliximab]; Enbrel® [etanercept]). Currently, there are five anti-TNF innovator molecules on the market (the three additional ones are Humira® [adalimumamb], Cimzia® [certolizumab] and Simponi® [golimumab]). The original infliximab label and subsequent updates mentioned that patients with long duration of Crohn's disease and chronic exposure to immunosuppressant therapies are more prone to develop lymphomas. These labeling updates were driven by case reports of lymphomas, hepatosplenic T-cell lymphomas, skin cancers and Merkel cell carcinomas with different anti-TNFs, early meta-analyses of controlled trials (reviewed in Bongartz et al., 2006, 2009; Stone et al., 2006; Bongartz et al., 2009; Pozadzides and Pro, 2009) and registry data (Geborek et al., 2005; Wolfe and Michaud, 2007) that suggested an increased risk. Similar labels and updates were applied to the different anti-TNFs. However, the most recent meta-analyses do not indicate an overall increased cancer risk directly attributable to anti-TNFs (Mercer et al., 2013; Solomon et al., 2014). It is recognized that certain autoimmune diseases (e.g., rheumatoid arthritis) are associated with an increased risk and that the risk correlates with disease severity (Baecklund et al., 2006), which complicates the interpretation of the epidemiology data.

A review of the TNF biology (Lebrec et al., 2015) indicates that