Studying Cancer as an Adverse Outcome From Nononcological Therapies: Review of the Food and Drug Administration's Postmarketing Commitment Database

Kirk Midkiff, David Harris, Alicia Gilsenan, Elizabeth Andrews

RTI Health Solutions, Research Triangle Park, NC, United States

ABSTRACT

Background: Multiple stakeholders wish to know if medications increase the risk of cancer. Clinical trials and enhanced pharmacovigilance have limitations for studying cancer such as incomplete capture and high cost (for trials). Observational studies are used to characterize the risk of cancer but may be limited due to inadequate case identification, exposure assessment and data sources, particularly for rare cancers. The ability to link patients to existing national cancer outcome data could be an ideal solution.

Objective: Review postmarketing commitments (PMC) to identify ones that may benefit from collaboration with cancer registries in the US.

Methods: We reviewed the FDA PMC database to identify cancer outcomes under study in nononcological drugs. We reviewed drugs with a NDA/BLA approval date after 1994 and excluded drugs indicated for oncology treatments or supportive therapy or where an animal study or clinical trial was requested. We reviewed approval letters and other published material to characterize the therapeutic class, study design and method for identifying cancer.

Results: Forty-six PMCs for 33 different drug entities were identified from the following drug classes: Immunologic (n = 11), endocrine and metabolic (n = 8), dermatologic
(n = 3) and other (n = 11). The most common cancer for the 12 entities that had a boxed warning for cancer was lymphoma (n = 7), followed by thyroid C-cell tumor (n = 4), other malignancies (n = 4), skin cancer (n = 2) and osteosarcoma (n = 1). Study designs were not well described for all PMCs. Of the 46 PMCs, the most common method for identifying cancer was active surveillance of patients (n = 10). Two studies mentioned cancer registries for long-term follow-up.

Conclusions: Postmarketing drug safety studies require the ability to properly identify and classify cancer outcomes over long periods. Linking treated cohorts from postapproval registries, database studies or clinical trials to cancer registries at a national level could provide a scientifically robust way to efficiently and accurately quantify cancer risk.

BACKGROUND

- Multiple stakeholders, including patients, clinicians, industry, and regulators, are concerned about the influence of medications on the development of cancer.
  - Cancer safety signals may appear during any phase of the drug development life cycle (preclinical, clinical, and postmarketing).
  - Signals that are observed prior to approval (e.g., in vitro, animal toxicology studies, and clinical trial experience) are typically reported on the drug label, and approval generally carries a requirement to further evaluate the signal.
  - Clinical trials have limitations for studying cancer, such as use of restricted populations, small numbers of patients, and exposure and follow-up of short duration.
  - The lag time between treatment and cancer diagnosis makes it less likely that routine and enhanced pharmacovigilance activities will identify potential treatment associations with a cancer outcome.
- Postapproval observational (noninterventional) studies may provide the best opportunity to characterize the risk of cancer as an adverse outcome.
  - Patient registries, cohort studies, and retrospective claims database analysis are frequently used. However, patient registries are limited by short durations of follow-up (e.g., usually < 10 years) and high dropout rates. Commercial claims databases usually have a short average period of follow-up (< 3 years) and incomplete ascertainment and classification of cancers. The ability to link patients to existing high-quality cancer outcome data from cancer registries could lead to high ascertainment of incident cancer cases over long periods of follow-up and with accurate case classification.
- The extent to which cancer registry data are used and may benefit postapproval studies is of interest to the authors.

Characteristics of US Cancer Registries

- Cancer reporting is mandatory in all states of the United States (US).
- Registries collect cancer diagnoses for over 96% of the US population.[1,2]
- Registries receive reports from physicians, treatment and radiation facilities, hospitals, and pathology laboratories. Registries reconcile case reports from these sources and capture the first course of treatment following diagnosis. They capture and code cancer diagnosis in International Classification of Diseases for Oncology (ICD-O) format characterizing topography, morphology, and behavior (more specific than ICD coding).

OBJECTIVE

- To review the Food and Drug Administration (FDA) postmarketing commitments (PMCs) and identify ones that may benefit from collaboration with cancer registries in the US.

METHODS

- We reviewed the FDA PMC database[3] (updated October 2014) to identify cancer outcomes under study in nononcological products, including drugs and biologics.
  - Inclusion criteria: Medications having a PMC with a cancer outcome and a new drug application (NDA) approval after 1994 or a biologic license application approval date after 1994
  - Exclusion criteria
    - Medications with an indication for oncology treatments or supportive therapy
    - Any study that was not an observational or enhanced pharmacovigilance study
- For those medications not excluded during the initial screen, we supplemented our review by reviewing the approved product label for treatment indication and for information regarding carcinogenicity, and regulatory approval letters for additional background on the origin of the safety concern and additional details of observational study designs. We reviewed, when possible, other publicly available material (i.e., clinicaltrials.gov website or targeted search of literature) to identify the type of cancer outcome under study, study design, and the method of case ascertainment.
- Using a simple descriptive analysis, we characterized the number of PMCs found for nononcology products, the treatment indication, the cancer outcome under study, the origin of the safety concern, the type of observational study design used, and the method for ascertaining cancer.
- We also summarized these results by therapeutic class, whether the product label included a black-box warning for the cancer under evaluation, and the most frequent types of cancers under study in this group of products.

RESULTS

- As of September 2014 for drugs and biologics approved after 1994, we identified 46 PMCs with a cancer outcome for nononcological therapy.
  - Thirty-three (72%) were unique drug entities (Table 1).
    - The most common drug or biologic class under study in the postmarketing setting was immunologic treatments (n = 11 [33%]) (Table 2).
    - **Of the 33 unique entities, 12 had a black-box warning in the product label for cancer. The most frequent type of cancer in the warning was lymphoma (n = 7) followed by thyroid C-cell tumor (n = 4), other malignancies (n = 4), skin cancer (n = 2) and osteosarcoma (n = 1).**
    - The origin of the cancer safety concern among these 33 unique entities was most frequently clinical trials (n = 14 [42%]) or preclinical rodent studies (n = 14 [42%]).
- Among the 46 PMCs, the most common method for identifying cancer was direct patient follow-up, either through a regular clinical visit to a study doctor (6-month or annual intervals) or direct patient telephonic/questionnaire contact (n = 13 [28%]).
- Among the 46 PMCs, a total of 12 (26%) PMCs were collaborating with cancer registries to identify the cancer outcome of interest.
  - Of those 12 PMCs, half were being conducted as two studies within a single cancer registry (Kaiser Permanente Northern California) in the US for pioglitazone- or pantoprazole-containing products.
  - The remaining 6 PMCs were being conducted as three separate study collaborations with cancer registries throughout the US (willing to participate) for teriparatide (n = 2 separate studies) or glucagon-like peptide 1 (GLP-1) agonists (n = 1 [i.e., a single study of 4 unique drugs]).
- A total of 33 (72%) PMCs may have limited patient follow-up, be missing cases due to incomplete follow-up, and/or have inconclusive characterization of the cancer diagnosis. One additional PMC was being carried out using a Nordic database.
- The average length of follow-up for cancer among unique studies that made any mention of the length of patient follow-up (n = 34 studies) was 8 years.

Table 1. Postmarketing Commitments for Nononcology Treatments Approved After 1994 With a Requirement to Assess a Cancer Outcome

Drug (Generic)	Indication	Origin of Signal	Study Type	Cancer Type Under Study	Source for Cancer Identification
Infliximab	CD, RA, UC, PsA, Ps, AS	Clinical trials and postmarketing reports	Pediatric CD registry	All	Clinical f/u
Infliximab	CD, RA, UC, PsA, Ps, AS	Clinical trials and postmarketing reports	Adult psoriasis registry	All	Clinical f/u
Etanercept	RA, psoriasis, JIA, AS	Clinical trials of TNF-blockers	Prospective surveillance study	All	Clinical f/u
Adalimumab	CD, RA, JIA, PsA, AS, Ps, UC	Clinical trials of TNF-blockers	Adult UC registry	All (focus on lymphoma)	Not stated
Adalimumab	CD, RA, JIA, PsA, AS, Ps, UC	Clinical trials of TNF-blockers	Adult psoriasis registry	All (focus on lymphoma)	Clinical f/u
Certolizumab pegol	CD, RA, PsA, AS	Clinical trials of TNF-blockers	Adult RA registry	All (focus on lymphoma)	Clinical f/u
Vedolizumab	CD, UC	Clinical trials	Prospective cohort study	All (secondary outcome)	Not stated
Ustekinumab	Psoriasis, PsA	Clinical trials and rodent studies	Database study	All	Nordic database
Ustekinumab	Psoriasis, PsA	Clinical trials and rodent studies	Psoriasis registry	All	Clinical f/u
Abatacept	RA, JIA	Clinical trials and rodent studies	RA registry	All	Questionnaire or telephone f/u
Abatacept	RA, JIA	Clinical trials and rodent studies	Pediatric JIA registry	All	Questionnaire or telephone f/u
Leflunomide	RA	Not stated	Case-controlled registry	All	Not stated
Fingolimod HCl	MS	Clinical trials	Prospective cohort study	All (focus on lymphoma)	Not stated
Dimethyl fumarate	MS	Rodent studies	Registry	Renal cell	Not stated
Pioglitazone[a]	Type 2 diabetes	Preclinical, clinical trials, observational study of pioglitazone	Prospective cohort study	Bladder	**Cancer registry (KPNC)**
Pantoprazole[b]	Erosive esophagitis related to GERD, Zollinger-Ellison syndrome	Rodent studies	Prospective cohort study	Gastric (from label)	**Cancer registry (KPNC)**
Tacrolimus	AD	Rodent studies	Pediatric AD registry	Skin or lymphoma	Questionnaire or f/u via physician office visit
Pimecrolimus	AD	Rodent studies	Pediatric and adult AD registry	Lymphoma, thyroid cancer, and cutaneous malignancies	Not stated
Teriparatide	Osteoporosis	Preclinical	Adult case-series surveillance study	Osteosarcoma	**Cancer registries**
Teriparatide	Osteoporosis	Preclinical	Prospective cohort study	Osteosarcoma	**Cancer registries**
Carbidopa/levodopa/entacapone	Parkinson's	Epidemiology studies	Database study	Prostate	Not stated
Omalizumab	Asthma, idiopathic urticaria	Clinical studies	Prospective cohort study	All	Not stated
Calcipotriene (betamethasone)	Psoriasis	Not stated	Not stated	All	Not stated
Eculizumab	Paroxysmal nocturnal hemoglobinuria, aHUS	Not stated	aHUS registry	All	Patient f/u
Maraviroc	HIV	Not stated	Prospective cohort study	All	Patient f/u
Romiplostim	Chronic immune thrombocytopenia	Clinical trials	Pregnancy registry[c]	All	Not stated
Romiplostim	Chronic immune thrombocytopenia	Clinical trials	Pregnancy registry[c]	All	Patient f/u
Eltrombopag	Thrombocytopenia and aplastic anemia	Not stated	Pregnancy registry[c]	All	Patient f/u
Exenatide[b]	Type 2 diabetes	Rodent studies and postmarketing reports	Prospective cohort study	Pancreas and thyroid	Claims
Exenatide LAR	Type 2 diabetes	Rodent studies	Case-series surveillance	Medullary thyroid cancer	**Cancer registries**
Albiglutide	Type 2 diabetes	Other GLP-1 agonist drugs/studies	Case-series surveillance	Medullary thyroid cancer	**Cancer registries**
Dulaglutide	Type 2 diabetes	Rodent studies	Case-series surveillance	Medullary thyroid cancer	**Cancer registries**
Liraglutide [rDNA origin] injection	Type 2 diabetes	Rodent studies	Case-series surveillance	Medullary thyroid cancer	**Cancer registries**
Liraglutide [rDNA origin] injection	Type 2 diabetes	Rodent studies	Database study	Thyroid	Claims
Teduglutide	Short bowel syndrome	Animal studies and clinical trials	Registry	Colorectal	Clinical f/u
Tesamorelin for injection	HIV with lipodystrophy	Not stated	Prospective cohort study	All	Not stated
Metreleptin	Lipodystrophy	Clinical trials	Registry	T-cell lymphoma	Not stated
Mirabegron	Overactive bladder	Not stated	Database study	All	Not stated
Lomitapide mesylate	Hypercholesterolemia with homozygous familial hypercholesterolemia	Rodent studies	Registry	Small bowel and hepatic	Not stated
Mipomersen sodium	Hypercholesterolemia with homozygous familial hypercholesterolemia	Rodent studies	Registry	Hepatocellular	Not stated
Azficel-T	Nasolabial fold wrinkles in adults	Clinical trials (1 case)	Registry	Skin cancer	Not stated

AD = atopic dermatitis; aHUS = atypical hemolytic uremic syndrome; AS = ankylosing spondylitis; CD = Crohn's disease; f/u = follow-up; GERD = gastroesophageal reflux disease; HIV = human immunodeficiency virus; JIA = juvenile idiopathic arthritis; MS = multiple sclerosis; Ps = plaque psoriasis; PsA = psoriatic arthritis; RA = rheumatoid arthritis; TNF = tumor necrosis factor; UC = ulcerative colitis.

[a] Four separate mentions in the PMC database, one for each formulation, corresponding to a single study.

[b] Two separate mentions in the PMC database, corresponding to a single study.

[c] Pregnancy exposure registries to "compare the maternal and fetal outcomes of patients exposed to specified treatment with outcomes of those not exposed to treatment" to detect "...neoplasm formation."

Table 2. Distribution of Therapeutic Class Among Unique Nononcological Therapies With a Cancer Outcome Under Evaluation as a PMC (N = 33)

Therapeutic Class	n	%
Immunologic[a]	11	33
Endocrine and metabolic[b]	8	24
Dermatologic[c]	3	9
Cardiovascular	2	6
Gastrointestinal	2	6
Hematological	2	6
Other	5	15

[a] Five therapies in this class are disease-modifying antirheumatic treatments.

[b] Four therapies in this class are GLP-1 agonists.

[c] Two therapies in this class are topical calcineurin inhibitors.

CONCLUSIONS

- Postmarketing drug safety studies of cancer outcomes should be able to identify and properly classify cancer outcomes over long periods of follow-up, but many existing studies appear weak in these design features.
- **We did not find evidence of widespread use of cancer registry data to identify and classify cancer outcomes in PMCs of nononcological drugs or biologics approved since 1994.**
- Based on the information available within the FDA PMC database and clinicaltrials.gov website, many more studies may benefit from collaboration with cancer registries to identify cancer outcomes of interest.

REFERENCES

1. Centers for Disease Control and Prevention. National Program of Cancer Registries (NPCR). 2013. Available at: http://www.cdc.gov/cancer/npcr/about.htm. Accessed July 27, 2015.
2. National Cancer Institute. Overview of the SEER Program. 2015. Available at: http://seer.cancer.gov/about/overview.html. Accessed July 27, 2015.
3. FDA. Postmarketing requirements and commitments: downloadable database file. May 20, 2015. Available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PostmarketingPhaseIVCommitments/ucm070777.htm. Accessed July 27, 2015.

CONFLICT OF INTEREST STATEMENT

- There are no conflicts of interest.

CONTACT INFORMATION

Kirk Midkiff, MPH
Director, Epidemiology

RTI Health Solutions
200 Park Offices Drive
Research Triangle Park, NC 27709

Phone: +1.919.541.6638
Fax: +1.919.541.7222
E-mail: kmidkiff@rti.org

The power of **knowledge**.
The value of **understanding**.

Presented at: 31st International Conference on Pharmacoepidemiology & Therapeutic Risk Management, August 22-26, 2015, Boston, MA, United States