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Adverse Renal Effects of Novel Molecular Oncologic Targeted Therapies: A Narrative Review

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Novel targeted anti-cancer therapies have resulted in improvement in patient survival compared to standard chemotherapy. Renal toxicities of targeted agents are increasingly being recognized. The incidence, severity, and pattern of renal toxicities may vary according to the respective target of the drug. Here we review the adverse renal effects associated with a selection of currently approved targeted cancer therapies, directed to EGFR, HER2, BRAF, MEK, ALK, PD1/PDL1, CTLA-4, and novel agents targeted to VEGF/R and TKIs. In summary, electrolyte disorders, renal impairment and hypertension are the most commonly reported events. Of the novel targeted agents, ipilumumab and cetuximab have the most nephrotoxic events reported. The early diagnosis and prompt recognition of these renal adverse events are essential for the general nephrologist taking care of these patients.

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In the past decade, advances in cell biology have led to development of anticancer agents that target specific molecular pathways. The National Cancer Institute (NCI) defines targeted therapies as "drugs or substances that block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression."[1] Targeted therapies are commonly used in cancer treatment, and it is vital that their renal toxicities be recognized and investigated. Adverse renal effects of targeted therapies occur through several complex mechanisms. Wide ranges of toxicities affecting various parts of the nephron have been reported with the novel targeted therapies. Recognition of adverse renal effects of these agents in a timely manner is extremely important for optimal patient care. Table 1 summarizes the oncological indications for the major targeted therapies discussed in this review. Figure 1 summarizes the renal toxicities that are associated with novel classes of targeted therapies and their effects on various parts of the nephron.

FDA ADVERSE REPORTING SYSTEM REVIEW

A recent study by our group had reviewed the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) data from 2011 to 2015 and found a high number of renal adverse events with novel targeted therapies.[2] The total number of renal adverse events reported was 2943. Of the 3 categories of events, 1390 (47.3%) were metabolic disturbances, 1243 (42.2%) were renal impairment, and 310 (10.5%) were hypertension (HTN). Ipilumumab and cetuximab, with 508 and 467 events respectively, were the most common targeted therapies associated with reported nephrotoxicities. The rate of adverse events were similar between men (n = 1369) and women (n = 1305).[2] Renal impairment was reported in 636 men and 522 women ($P < 0.001$). Metabolic disturbances were reported in 620 men and 639 women ($P = 0.5$). HTN was reported with 113 men and 144 women ($P = 0.053$).[2] The most common electrolyte abnormality was hypokalemia (n = 539). This analysis indicates that electrolyte abnormalities are the most common renal or metabolic toxicity. Overall, for all renal events, there was no difference in the incidence between men and women. However, men seem to have a higher risk of

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Table 1. Approved hematology and oncology indications for targeted therapies along with dosing in CKD and ESRD

Generic name of targeted therapy (trade name)	Target	Cancer	Renal excretion	Dose adjustment for GFR 30–90 ml/min/1.73 m^2	Dialysis dose adjustment
Afatineb (Gilotrif)	EGFR TKI	Metastatic NSCLC	<5%	No	No data
Axitinib (Inlyta)	Multi target TKI	Pancreatic cancer, RCC, CML	<25%	No	No
Aflibercept (Eylea or Zaltrap)	VEGF	Colorectal cancer	No	No	No
Bevacizumab (Avastin)	VEGF	Colorectal cancer, NSCLC, RCC, breast cancer, epithelial ovarian cancer, GBM	No	No	No
Bosutinib (Bosulif)	BCR-ABL TKI	CML	No	Reduce dose to 300 mg once daily	No data
Cetuximab (Erbitux)	EGFR	Colorectal cancer, head and neck SCC	No	No	No
Crizotinib (Xalkori)	ALK	NSCLC	No	No	No
Dabrafenib (Tafinlar)	BRAF	Melanoma	<25%	No	No data
Dasatinib (Sprycel)	BCR-ABL TKI	CML	<5%	No	No data
Erlotinib (Tarceva)	EGFR TKI	NSCLC, pancreatic cancer	<10%	No	No
Gefitinib (Iressa)	EGFR TKI	NSCLC	<5%	No	No
Ibrutinib (Imbruvica)	Bruton kinase TKI	CLL, mantle cell lymphoma	No	No data	No data
Imatinib (Gleevac)	BCR-ABL TKI	Gastrointestinal stromal tumors, CML	<15%	No	No
Ipilimumab (Yervoy)	CTLA4	Melanoma	No	No	No data
Lapatinib (Tykerb)	ERBB2	Breast cancer	<5%	No	No
Nivolumab (Opdivo)	PD-1	Melanoma, NSCLC, Hodgkin lymphoma, RCC	No	No	No data
Nilotinib (Tasigna)	BCR-ABL TKI	CML	No	No	No data
Panitumumab (Vectibix)	EGFR	Colorectal cancer	No	No	No
Pazopanib (Votrient)	Multitarget TKI	RCC, soft tissue sarcoma	<4%	No	No
Pembrolizumab (Keytruda)	PD-L1	Melanoma, NSCLC, Hodgkin lymphoma	No data	No	No
Pertuzumab (Perjeta)	ERBB2	Breast cancer	No	No	No data
Ponatanib (Iclusig)	BCR-ABL TKI	CML, ALL	No	No	No data
Regorafenib (Stivarga)	Multitarget TKI	Colorectal cancer, gastrointestinal stromal tumors	<20%	No	No
Sorafenib (Nexavar)	Multitarget TKI	RCC, hepatocellular carcinoma, thyroid carcinoma	<20%	No	No
Sunitinib (Sutent)	Multitarget TKI	RCC, gastrointestinal stromal tumors, pancreatic neuroendocrine tumors	<20%	No	No
Trametinib (Mekinist)	MEK	Melanoma	<20%	No	No data
Trastuzumab (Herceptin)	ERBB2	Breast cancer	No	No	No
Vandetanib (Caprelsa)	Multitarget TKI	Medullary thyroid cancer	<25%	No	No data
Vemurafenib (Zelboraf)	BRAF	Melanoma, thyroid cancer, colorectal cancer	<5%	No	No data

ALK, anaplastic lymphoma kinase; ALL, acute lymphocytic leukemia; BCR-ABL, breakpoint cluster region–abelson; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CTLA, cytotoxic T lymphocyte antigen−4; EGFR, epidermal growth factor receptor; GBM, gliobastoma multiforme; MEK, mitogen-activated protein kinase; NSCLC, non−small-cell lung cancer; PD, programmed cell death; RCC, renal cell carcinoma; SCC, squamous cell cancer; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.
Information obtained from package inserts of agents, clinical trials, and published case reports.
No data available for most agents for dose adjustments for GFR < 30 ml/min/1.73 m^2 except vandetanib, which requires dose adjustment.

developing renal impairment with targeted therapies compared to women. No such gender difference exists in standard chemotherapy-related acute kidney injury (AKI). There was no difference in gender for electrolyte disorders and HTN associated with targeted therapies.[2] Hypokalemia, hypophosphatemia, hypomagnesemia, and hyponatremia are concerns in patients receiving targeted therapies.

There are important limitations that one must keep in mind when using the FAERS database. The events are reported by providers and/or patients and therefore could have a reporting bias. In addition, not all demographic and comorbidity information is available to help identify whether other nephrotoxic risk factors are present, such as use of nonsteroidal anti-inflammatory agents, history of HTN or diabetes mellitus, known chronic kidney disease (CKD), recent use of contrast agent, or recent use of standard chemotherapy that could be nephrotoxic. Most importantly, it is not possible to determine whether an event is truly caused by the drug as opposed to the underlying disease or concomitant medications or by prior chemotherapies administered to these patients. In addition, we cannot get an accurate assessment of incidence rate, as we do not have complete information on the total number of patients who have actually received these agents.

In this narrative review, we discuss the renal adverse events of a few novel anti−vascular endothelial growth factor (VEGF) and tyrosine kinase inhibitors (TKI) but focus more on the other novel targeted therapies used in cancer patients. We also compare the published renal adverse data to the FDA-reported events, providing a comprehensive overview on the toxicities.

VEGF AND VEGF RECEPTOR BLOCKADE

A hypothesis that tumor growth is angiogenesis dependent led to the development of antiangiogenic drugs.[3] These drugs target the VEGF or VEGF receptor