Drug induced malignancy: a focus on pioglitazone

Abstract

In this perspective I’ll list the most common currently available carcinogenic and potentially carcinogenic drugs and I’ll grant a detailed focus to the tale of the antidiabetic pioglitazone; a drug withdrawn or heavily restricted in the developed countries while widely prescribed and utilized in the Afro-Asian developing ones.

Available carcinogenic drugs

Some common available carcinogenic and potentially carcinogenic drugs include: Alkyllating and platinum based antineoplastic agents e.g. cyclophosphamide and cisplatin; topoisomerase II inhibitors e.g. etoposide and anthracyclines e.g. doxorubicin which inhibit DNA repair as well as radiotherapy may cause secondary cancer especially myelodysplastic syndrome and acute myelogenous leukemia and the ten-year incidence is approximately 1.5% and the risk gets higher with higher drug doses, longer treatment time. Further, the selective B-Raf kinase inhibitors vemurafenib and dabrafenib which revolutionized the treatment of melanoma were reported to increase the risk of squamous cell carcinoma of the skin. They’ve paradoxically activated the MAP kinase pathway in BRAF wild-type cells, leading to secondary malignancies. Combined oral estrogen progesterone therapy was associated with an increased risk of breast cancer development in postmenopausal women whereas estrogen therapy used without progesterone in post-menopausal women with an intact uterus was found to increase the risk of developing endometrial cancer. Immunosuppressant’s like tumor necrosis factor inhibitors e.g. adalimumab or thiopurines e.g. azathioprine are reported for increased risk to develop lymphoma or skin cancer among other malignancies and their use must be governed with the risk benefit conceptual model. Liraglutide, an anti-diabetic and anti-obesity drug, was also linked with a potential increased risk of thyroid medullary carcinoma and/or pancreatic cancer. Moreover, dapagliflozin, the first in class SGL-2 inhibitors has been reported to have a potential to increase the incidence of bladder and breast cancer, for this reason it was rejected by the U.S. Food and Drug Administration (FDA) in 2012 to be approved 2 years later after the two developing companies provided more data to exclude the significance of this potential.

Pioglitazone causation of bladder cancer

Pioglitazone (PIOG) is a thiazolidinedione that is used for the treatment of type 2 diabetes mellitus by activating the nuclear receptor PPARγ. His counterparts troglitazone was withdrawn in 1997, 2 months after its launch, from UK and three years later in US; rosiglitazone was withdrawn in UK and EU in 2010 ten years after its launch; but these ‘re other tales to tell. On May 2014, an Egyptian PhD student was studying in preparation to finish his final PhD exams and he was amazed when he read in the 2012 twelfth edition of the well-known Katzung & Trevor’s Basic and Clinical Pharmacology textbook: “the risk of bladder cancer appears to be cumulatively increased with high doses of PIOG” to be followed after few lines that because of toxicities the FDA restrict rosiglitazone to small populations including some American patients who don’t wish to be on PIOG or a PIOG containing drug”. He decided to search the literature, his wonder was confirmed and he’s published his first single author paper describing the widespread usage of PIOG in his country as well as most of the developing countries as “the prefect crime of the new millennium.”

PIOG and bladder cancer from association to causation

Some of the evidence collected and presented with its relevant references in that paper was: On July 15, 1999 PIOG was approved by FDA. Preclinical studies have showed that bladder tumors were observed in male rats receiving doses of PIOG that produced blood drug levels equivalent to those resulting from a clinical dose. In 2005 some scientists noticed a possible relationship between PIOG and bladder cancer from association to causation.
Drug induced malignancy: a focus on pioglitazone

In 2012, Canadian authors after reviewing and performing some meta-analysis studies wrote a conclusion that exposure to PIOG is associated with an increased risk of bladder cancer and they’ve also stressed the inference of causality between the larger cumulative doses and longer duration of PIOG use and the greater risks of bladder cancer. Also in 2012, another meta-analysis that involved five studies included 2 350 908 diabetic patients showed PIOG to be associated with a significantly higher risk of bladder cancer and informed that early stoppage of PIOG is highly likely to abolish this potential. The relative risk for bladder cancer in patients with 12-24 months of PIOG use was shown to be 1.34 and was even stronger, 1.38, for duration >24 months. In 2013, six studies involving 215 142 patients using PIOG, with a median period of follow-up of 44 months revealed that the hazard of developing bladder cancer was significantly higher in patients using PIOG (hazard ratio 1.23; 95% CI) compared with control groups. Also, in 2013, other authors have showed that even a relatively short duration of PIOG treatment was associated with the occurrence of bladder cancer (5 months treatment in a current smoker 60 X 40 years patient).

A call to intervene and protect innocents

In 2015, a year after the mentioned Egyptian researcher, already got his PhD, has published his perspective he read: “No link found between bladder cancer and use of PIOG” as a leading piece of news in lots of newspapers worldwide which praised the results of an independent cohort study made by a large research consortium as the official in-front the audience including foreign international experts of his repeated official calls to suspend or restrict PIOG in Egypt to save the innocent ignorant patients who have been denied their right to know the risk and/or to choose any of the relatively safer available alternatives if they wish as even the black box warning was not even added to the Arabic pamphlet inside PIOG packages! The Egyptian official was very indiscriminate while listening and with an apathic look he’s answered the researcher: “Be Pragmatic, we’re not even added to the Arabic pamphlet inside PIOG packages! The Egyptian official was very indiscriminate while listening and with an apathic look he’s answered the researcher: “Be Pragmatic, we’re strong enough to judge whether the potentially carcinogenic drugs in EU or US have the same potential in Egypt or not!” And he refused, and still, even to oblige the related companies to add the US black box warning showing this carcinogenic potential but in Arabic.

“...the human is the same in Egypt as in EU or US,” the researcher replied and left the conference immediately to show disguise and recently in 2018, he’s published a paper declaring that he can’t and will never be pragmatic! Some of the evidence collected and presented in that paper was: In 2017, another metaanalysis confirmed that PIOG increased the risk for bladder cancer especially in European patients who undergo treatment with PIOG for longer durations (>12 months) or are administrated a larger cumulative dose (>28,000mg). In 2018, researchers have reconfirmed the elevated bladder cancer risk emerged within the first 2 years of PIOG treatment, compared with DPP-4s and sulfonylureas, and the cancer risk was attenuated after discontinuing PIOG compared with patients treated with PIOG for more than 2 years. In 2018, researchers have also confirmed evidence suggesting that PIOG may increase the risk of bladder cancer, possibly in a dose- and time-dependent manner and have also pointed to the miserable remark...
that this association differs with the source of funding (sponsored by industry or not). At the end of this perspective, I’d like to remind that in 2014, Takeda, the inventor and main manufacturer of PIOG announced the 10-year data from a longitudinal cohort study that it said showed no risk for bladder cancer associated with PIOG. Apparently, these results submitted by Takeda couldn’t convince a judge and a Jury in Louisiana who awarded in the same year a New York patient who developed bladder cancer while taking PIOG 9 billion US dollars.

On April 2015, Takeda announced that it has reached a settlement agreement expected to resolve most lawsuits related to PIOG that were pending in the US. The settlement was deemed final and official in September 2015, after over 96% of claimants chose to enter into the settlement, thereby triggering a $US2.37 billion payments by Takeda. Noteworthy, in 2008, PIOG was the tenth best-selling drug in the U.S. with sales exceeding $2.4 billion. In 2018, a clinical phase III trial testing PIOG for Alzheimer’s treatment was early ended by Takeda on January 2018 due to poor outcomes and its sales are estimated to be maximally 25 million in the U.S. Unfortunately, its main sales are in Asia, Africa and the developing countries (21) where instead of love, faithfulness, righteousness and peace praised by sons of Korah in Psalm 85 one may sadly rephrase the tenth verse to be: “Ignorance and greed meet together; cruelness and misery kiss each other” and till this moment PIOG is still widely prescribed without restrictions or to which I can’t be pragmatic!


drugs to which I can’t be pragmatic!


Conflict of interest

The author declares that there is no conflict of interest.

Acknowledgements

None.

References


