

# 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and potentially carcinogenic drugs and I'll grant a detailed focus to the tale of the antidiabetic pioglitazone; a drug withdrawn or heavily restricted in the developed countries while widely prescribed and utilized in the Afro-Asian developing ones.

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## History of drug-cancer associations

Pharmacovigilance of the potential carcinogenic effects of drugs has a long history; in 1980, Schmahl and Habs<sup>1</sup> have written: "The physician using drugs has been trained to take acute and subacute toxic side effects of drugs into consideration; nowadays he ought to expand this caution to possible chronic toxicity including carcinogenicity" They've wisely advised that such potentially carcinogenic drug should be considered only "if the case has a poor prognosis or there is no alternative to this therapy".<sup>1</sup> They've also added: "If, however, this is not so, then the physician has to consider whether the potentially hazardous drug should be administered or whether alternatives are at hand". In 1981, Hoover & Fraumeni<sup>2</sup> wrote a review in *Journal of Cancer* and they've mentioned: "The detection of drug-cancer associations not only influences clinical and public health practice but may also provide insights into mechanisms of carcinogenesis". They've also brilliantly added: "The clinician contributes to the prevention of drug-induced cancer by being alert to iatrogenic hazards and cooperating in epidemiologic investigations, by weighing risks versus benefits in individual cases, and by discussing with patients the rationale and risks of proposed forms of therapy".<sup>2</sup>

## Available carcinogenic drugs

Some common available carcinogenic and potentially carcinogenic drugs include: Alkylating 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.<sup>3,4</sup> 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.<sup>5,6</sup> 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.<sup>7,8</sup> 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.<sup>9,10</sup> Liraglutide, an anti-diabetic and anti-obesity drug, was also linked with a potential increased risk of thyroid medullary carcinoma and/or pancreatic cancer.<sup>11</sup> 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.<sup>12,13</sup>

## 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 PPAR $\gamma$ . His counterparts troglitazone was withdrawn in 1997, 2 months after its launch, from UK and three years later in US;<sup>14</sup> rosiglitazone was withdrawn in UK and EU in 2010 ten years after its launch;<sup>15</sup> 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".<sup>16</sup>

## 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 neoplasm in humans as they noted more cases (14 vs 6; P=0.069) of bladder neoplasm in the PIOG versus placebo arms in

the PRO active study. On June 2011 the French Agency for the Safety of Health Products and the Germany's Federal Institute for Drugs and Medical Devices have decided to withdraw PIOG from France and Germany, respectively regarding high risk of bladder cancer. Mauritius, Lebanon, Tunisia, Algeria and Morocco have followed France decision and withdrawn PIOG from their market on the same month. On June 15, 2011 the U.S. FDA has officially announced that PIOG use for more than one year may be associated with an increased risk of bladder cancer; later the label was updated with an additional warning about this risk and on July 2011 a similar alert was released from the European Medicines Agency but with no withdrawal of the drug. However, since that date and onwards, restrictions to its use have been evolving fast and rigid in the developed countries.

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 stated in the news! These pieces of news have provoked him to analyze and criticize these results as well as to publish another paper showing the presumed "independence" to be an illusion as he believes and as revealed by the declaration of interests made by the authors of the pro PIOG study showing research support from the related pharmaceutical companies and even one of the major researchers had a membership in a speaker's bureau of one of them. He added at the end of his article: "I don't doubt the honesty of fellow colleagues, God forbids but I only admit the logic human suspicion knowing that even the saints among us are tempted". Further, he asked for an intervention: "Thus, humbly, I ask all scientists in the developed world to work together to oblige the FDA and all similar agencies to establish a new mechanism by which the large pharmaceutical companies become forced to fund "real" independent research center(s) not chosen by or related in any way to the pharmaceutical companies and their products".<sup>17</sup>

Again, in 2016 and in the British Medical Journal (BMJ) the Egyptian researcher has read once again: "there's no evidence of an association between ever use of PIOG and risk of bladder cancer compared with never use". He's just moved to the end of the article to

find out that the research was supported by the main pharmaceutical company of PIOG; Takeda and that almost all of the authors are employed by institutes that are financially connected with Takeda and other concerned pharmaceutical companies and also one of the authors was employed by Takeda.<sup>18</sup> However, also in 2016 and in the same BMJ another article was published by Marco and colleagues who revealed that use of PIOG for 1 year or less, 1-2 years, and more than 2 years was associated with a 33%, 66%, and 78% increased risk of bladder cancer, respectively. At the end of this article, one will find that the research was funded by a Canadian real independent institute with no relation of whatever with the pharmaceutical companies or any other organization that might have an interest in the research results.<sup>19</sup>

### You may scream for the innocents, but nothing would change

Since he first noticed the risk, the Egyptian researcher has addressed nearly all the concerned authorities in Egypt to withdraw or restrict the use of PIOG as most of the patients using it have no idea about the possible carcinogenic risk that led to rigid restrictions or prohibitions on its usage in the developed countries. He addressed the media and social networks in Egypt to help in his campaign and lots of journalist have helped but the results on the grounds remained unchanged, only minority of patients have read the newspapers or listened to a private TV show that addressed the subject and the majority remain in complete lack of knowledge about the risk, PIOG was and still heavily prescribed and utilized without restrictions. In 2016, he met a senior pharmacovigilance official in the Egyptian ministry of health at an international conference held in Cairo focusing on the pharmacovigilance concept. The researcher reminded 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 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!<sup>20</sup>

Some of the evidence collected and presented in that paper was: In 2017, another meta-analysis 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; cruelty and misery kiss each other" and till this moment PIOG is still widely prescribed without restrictions or warnings to millions of ignorant patients in my country as well as in most of the developing countries and no action is expected to change this misery, at least in the short term.

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## Conflict of interest

The author declares that there is no conflict of interest.

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