Title

Re: Use of Phosphodiesterase Type 5 Inhibitors for Erectile Dysfunction and Risk of Malignant Melanoma

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approach to estimations (eg, underestimation of side effects because of less frequent visits), and narrow time lines (eg, low patient accrual). The study by Retz and colleagues is particularly limited by a low power owing to a small patient number attributable to premature study closure because of insufficient accrual. In addition, only 66% of patients received vinflunine in the approved second-line setting. This underscores the accepted application of other biologically active systemic therapies in second-line therapy for metastatic UCB. Although other regimens are not officially EMA-approved, there are some effective therapeutic alternatives that warrant clinical awareness. Very recently, a retrospective analysis based on individual patient-level data from phase 2 trials of salvage systemic therapy demonstrated a significant overall survival improvement for taxane-containing combination chemotherapy [3]. In addition, several novel, targeted-therapy single agents and combination therapies have been investigated in phase 2 and phase 3 clinical trials, but only a minority demonstrated reasonable response rates and survival improvements [4]. Nevertheless, highly promising initial results for new immunotherapeutic strategies targeting the PD-1/PD-L1 axis indicate tremendous potential, with good tolerability for many patients. The PD-L1 antibody MPDL3280A recently received breakthrough therapy designation status from the US Food and Drug Administration [1].

The complex, heterogeneous tumor biology of UCB necessitates meticulous assessment of the mutational status of actionable mutations and stratification according to therapeutic biomarkers in future clinical trials investigating targeted agents. Selection of the right patients who will benefit the most from any individual treatment in the devastating second-line therapy situation is the most challenging goal.

Conflicts of interest: The authors have nothing to disclose.

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Re: Use of Phosphodiesterase Type 5 Inhibitors for Erectile Dysfunction and Risk of Malignant Melanoma
Loeb S, Folkvaljon Y, Lambe M, et al

JAMA 2015;313:2449–55

Experts' summary:
The authors conducted a nested case-control study using the Prostate Cancer Database Sweden and the Swedish Prescribed Drug Register to determine the association between phosphodiesterase type 5 (PDE5) inhibitor use and malignant melanoma [1]. Due to the observational study design, the authors used Hill's criteria to determine if the associations detected were causal [2].

A 21% higher odds of malignant melanoma was observed among men who had taken PDE5 inhibitors. However, this increased risk was observed only among men who filled one PDE inhibitor prescription, not those filling multiple prescriptions. Increased risk was seen only for superficial stage 0 melanoma, not higher stage disease. No associations were detected between longer half-life PDE5 inhibitors (particularly tadalafil) and melanoma, or between PDE5 inhibitors and higher-stage melanoma. Furthermore, a positive association was also identified between PDE5 inhibitors and basal cell carcinoma, which have totally different biology from melanoma, and for which there is no known biologic mechanism.

Experts' comments:
In their conclusion, the authors note the overall association and question whether the risk of malignant melanoma associated with PDE5 inhibitor use is causal. However, the pattern of these associations do more than raise questions about the causal relationship between use of PDE5 inhibitors and malignant melanoma; they almost certainly negate it—per the authors' own prespecified subanalyses. We are thus left with a statistically significant—but noncausal and likely clinically irrelevant—association. In the absence of any evidence of causality, the association between use of PDE5 inhibitors and an increased risk of melanoma is most likely due to ascertainment bias and/or unmeasured confounding. For example, men who obtain PDE5 inhibitor prescriptions are more likely to be seen by health care providers and thus are more likely have their skin observed, leading to the increased detection of low-stage melanoma. The same rationale likely explains the higher incidence of melanoma among married men—more eyes on their skin.

The problem here is that the subtleties of causal inference are often lost in the lay press and in the courtroom, and the conclusion that PDE5 inhibitor use is

associated with malignant melanoma and "may" be causal may prove sufficient to drive a wave of groundless, expensive lawsuits. Drug injury plaintiff attorneys certainly do not delve into dose-response relationships, temporality, or effect sizes, let alone unmeasured confounding. One example website already states: "The recent medical study finding which indicates an association between each of these PDE5 inhibitor drugs with invasive melanoma skin cancer might be of particular concern to patients that have used any of these drugs... We are currently investigating cases of melanoma in men who used Viagra, Cialis, Levitra..., as possible drug injury lawsuits" [3].

The effects of presenting this study as a positive association between PDE5 inhibitors and malignant melanoma despite lacking evidence of causality may have serious, deleterious consequences for patients who would benefit from, but may not be prescribed PDE5 inhibitors, as well as for physicians and society who may face an increased number of lawsuits generated not by sound evidence, but by groundless fear.

Conflicts of interest: The authors have nothing to disclose.

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