RESEARCH ARTICLE

Hypothyroidism Side Effect in Patients Treated with Sunitinib or Sorafenib: Clinical and Structural Analyses

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Abstract

Tyrosine kinase inhibitors (TKIs) provide more effective targeted treatments for cancer, but are subject to a variety of adverse effects, such as hypothyroidism. TKI-induced hypothyroidism is a highly complicated issue, because of not only the unrealized toxicological mechanisms, but also different incidences of individual TKI drugs. While sunitinib is suspected for causing thyroid dysfunction more often than other TKIs, sorafenib is believed to be less risky. Here we integrated clinical data and *in silico* drug-protein interactions to examine the pharmacological distinction between sunitinib and sorafenib. Statistical analysis on the FDA Adverse Event Reporting System (FAERS) confirmed that sunitinib is more concurrent with hypothyroidism than sorafenib, which was observed in both female and male patients. Then, we used docking method and identified 3 proteins specifically binding to sunitinib but not sorafenib, i.e., retinoid X receptor alpha, retinoic acid receptors beta and gamma. As potential off-targets of sunitinib, these proteins are well known to assemble with thyroid hormone receptors, which can explain the profound impact of sunitinib on thyroid function. Taken together, we established a strategy of integrated analysis on clinical records and drug off-targets, which can be applied to explore the molecular basis of various adverse drug reactions.

Introduction

Conventional chemotherapies usually do not discriminate tumor cells and other rapidly dividing normal cells, thus leading to unpredictable cytotoxic side effects. In contrast, targeted therapies specifically interfere with molecular targets located in tumor cells or involved in tumor growth. Therefore, targeted therapies may be particularly effective to those patients not reactive to cytotoxic agents. Also, targeted therapies may reduce certain toxicity related to cytotoxic agents (although causing other adverse effects as introduced below) [1]. Tyrosine-kinase inhibitors (TKIs) are a class of drugs mainly used in cancer treatment as targeted therapy [2]. Being analogues of ATP, TKIs typically compete with the ATP for binding site of particular oncogenic tyrosine kinases. By blocking the signaling pathways involved in the phosphorylation of

many key proteins in signal transduction cascades, TKIs can depress tumor cell survival and proliferation. Imatinib is the first TKI to be introduced into clinical oncology, which is followed by novel ones, including sorafenib [3] and sunitinib [4]. Sorafenib is an orally active multi-kinase inhibitor that is approved for the treatment of renal cell carcinoma, hepatocellular carcinoma and some other types of cancer. It inhibits several tyrosine protein kinases (e.g., VEGFR and PDGFR) and Raf kinases [5]. Sunitinib is another oral and multi-targeted TKI. It is approved by the FDA for the treatment of renal cell carcinoma, also as a second-line therapy for patients whose gastrointestinal stromal tumor is resistant to imatinib. Tyrosine kinases inhibited by sunitinib include VEGFR, PDGFR, KIT, FLT3, etc [6].

With the increased use of TKIs for cancer treatment, a variety of unusual adverse effects begin to emerge [7]. It is a puzzling phenomenon that while the TKIs achieve therapeutic effects through similar mechanisms of action, on the other hand, they differ dramatically in certain adverse effects. A typical example is TKI-induced hypothyroidism (i.e., deficiency of thyroid hormone), which is characterized by a number of symptoms, such as tiredness, poor ability to tolerate cold, and weight gain. Sunitinib, for instance, is suspected for causing thyroid dysfunction more often than other TKIs [8]. In contrast, the incidence of hypothyroidism in sorafenib user is reported to be much lower [9–11]. The possible toxicological difference between sunitinib and sorafenib raises our attention, because they may serve as a precious pair of case and control drugs. Since these two drugs are broadly similar in their actions, except for hypothyroidism side effect, if some minor differences are found, they are highly likely to be associated with the pathogenesis of the drug-induced hypothyroidism.

In the present study, we primarily retrieved a large number of clinical reports of patients using sunitinib or sorafenib (Table 1) from FDA Adverse Event Reporting System (FAERS), in order to calculate the frequency of hypothyroidism adverse events. In the United States, the FDA is the major agency that responsibie for monitoring the safety of marketed drug products. For this purpose, FDA has established FAERS to collect and restore reports of adverse events, which are mostly sent by healthcare professionals and patients directly to the FDA on a voluntary basis. Those reports suggesting significant signals of certain adverse events can raise special attention of not only FDA safety evaluators, but also researchers worldwide [12–14]. FDA used to release the data to the public quarterly, but an analysis requires researchers to manually download and preprocess the data for every quarter starting from 2004. In an effort to provide easier access to FAERS, the openFDA initiative (https://open.fda.gov/) is launched in June 2014, which gives the official API access to the raw data of adverse events reports in a structured and computer-readable format. In the present study, therefore, we were enabled to efficiently identify the significant difference between sunitinib and sorafenib.

In addition, the toxicological mechanisms of TKI-induced hypothyroidism remain largely unknown. Since sunitinib and sorafenib are proved to differ in the risk of causing

Table 1. Combined summary of sunitinib- and sorafenib-associated reports of adverse events.

		Sunitinib	Sorafenib
	Total	17242	9634
Sex	Female	5351 (31.03%)	2488 (25.83%)
	Male	10153 (58.89%)	6411 (66.55%)
	N/A	1738 (10.08%)	735 (7.63%)
Reproting Source	Health Professionals	11692 (67.81%)	7009 (72.75%)
	Consumers	4597 (26.66%)	1116 (11.58%)
	Lawyers	3 (0.02%)	1 (0.01%)
	N/A	950 (5.51%)	1508 (15.65%)

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hypothyroidism, we hypothesized that if a certain protein tends to be unexpectedly targeted by sunitinib but not sorafenib, that protein may serve as a sunitinib-specific off-target and a candidate mediator of sunitinib-induced hypothyroidism. Even it is unaffordable to experimentally search for such kind of off-targets among a great number proteins, we alternatively used the DRAR-CPI online server [15], which provided a free but highly efficient platform for *in silico* simulation of molecular structures and prediction of preferred orientation of drug-protein bindings. By examining the differences between sunitinib and sorafenib in their interaction profile towards a series of human proteins, several candidates were successfully highlighted, which may be associated with the underlying mechanisms of hypothyroidism side effect.

Results

Sunitinib co-occured with hypothyroidism events more frequently than sorafenib

Although sunitinib, as compared with sorafenib, has been suspected for higher risk of inducing hypothyroidism, the current clinical evidences were only based on relatively small samples with limited persuasiveness [9–11]. On the other hand, FAERS provided us with a unique opportunity to validate previous observations with a large sample of patients. We retrieved all the adverse events related to sunitinib and sorafenib, respectively (see Methods). To avoid the complication of drug-drug interaction, the patients using sunitinib and sorafenib simultaneously were excluded, thus leaving 17242 cases of sunitinib and 9634 of sorafenib. Hypothyroidism adverse reaction was reported in 1.66% of the sunitinib-related cases, while the same problem was found in only 0.57% of the sorafenib-related cases (Table 2). The one-tailed Fisher's exact test was performed to compare these two drugs, and the result suggested that the hypothyroidism reporting rate was significantly higher for sunitinib than sorafenib (P = 2.86E-16). Hence, FAERS data corroborated the specific association between hypothyroidism and sunitinib.

Higher risk of sunitinib than sorafenib regardless of sex factor

Gender difference in thyroid system function is a common medical knowledge [16]. Because of that, the etiology and prevalence of hypothyroidism naturally differ between female and male population, i.e., women are observed to be more affected by hypothyroidism than men [17–20]. Although drug-induced hypothyroidism is a type of side effect rather than a primary disease, in the context of this study, we are still cautious about the possible confounding effect of sex factor on the FAERS statistics. Therefore, we further compared the sunitinib and sorafenib for the reporting rate of hypothyroidism, with the female and male patients separated. As

Table 2. Test for the difference of the hypothyroidism reporting rate between sunitinib and sorafenib in the FDA adverse event reporting system (FAERS).

	Sunitinib	Sorafenib
Hypothyroidism Reported	287	55
Hypothyroidism Not Reported	16955	9579
Ratio of Hypothyroidism Report (%)	1.66	0.57
Odds Ratio (95% CI)	2.95 (2.21 – 3.94)	
P-value*	2.86E-16	

* One-tailed Fisher's exact test was performed for the higher rate of hypothyroidism for sunitinib compared to sorafenib.

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Table 3. The difference of the hypothyroidism reporting rate between sunitinib and sorafenib regarding female and male populations.

	Female		Male	
	Sunitinib	Sorafenib	Sunitinib	Sorafenib
Hypothyroidism Reported	119	18	138	35
Hypothyroidism Not Reported	5232	2470	10015	6376
Ratio of Hypothyroidism Report (%)	2.22	0.72	1.36	0.55
Odds Ratio (95% CI)	3.12 (1.90 – 5.14)		2.51 (1.73 – 3.64)	
P-value*	3.32E-07		1.28E-07	

* One-tailed Fisher's exact test was performed for the higher rate of hypothyroidism for sunitinib compared to sorafenib.

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suggested by the results (Table 3), sunitinib co-occurred with hypothyroidism events more frequently in both female and male patients. Even though the reporting odds ratio between sunitinib and sorafenib was higher in women than men, it did not suggest any significant sex difference ($P > 0.1$ for multivariate logistic regression, data not shown). Thus, we confirmed that the difference in hypothyroidism incidence between sunitinib and sorafenib users should be independent of sex factor and be mainly attributed to the unique toxicity of sunitinib.

Differences in target binding profile between sunitinib and sorafenib

The purpose of the above pharmacovigilance data analysis was not only to corroborate the relatively higher hypothyroidism risk of sunitinib, but more importantly to understand underlying toxicological mechanisms. Due to the complex nature of drug toxicity and limited knowledge about drug-induced hypothyroidism, it has always been extremely difficult to perform hypothesis-driven study on the detailed toxicological mechanisms. Because of that, we alternatively adopted a data-driven strategy and explored the potential off-targets specifically interacting with sunitinib but not sorafenib (Fig 1A), by using chemical-protein docking method [21,22] (see Methods). For this purpose, we uploaded the molecular structure information [23] of sunitinib and sorafenib into the DRAR-CPI server. The interaction strength of a drug molecule to a protein was primarily measured by docking score (i.e., the lower docking score, the stronger strength of binding). In addition, considering the relative strength based on the interaction matrix of a collection of drugs and proteins restored in DRAR-CPI, the raw docking score was further normalized into Z'-score, so as to address the endogenous variance among proteins or chemicals and increase data accuracy [24].

A total of 208 protein pockets were suitable for docking with both sunitinib and sorafenib molecules (S1 Dataset). We primarily calculated the Pearson's correlation coefficients (PCC) between Z'-score vectors of sunitinib and sorafenib across these 208 targets (Fig 1B). As two highly comparable drugs of the TKI class, sunitinib and sorafenib exhibited positively correlated protein binding profiles (PCC = 0.43, p = 1.30E-10), which underlined their overall similarity in target spectrum and pharmacology. We therefore hypothesized that the minor distinctions in protein binding affinity between them might account for the sunitinib-biased risk of hypothyroidism. Following this hypothesis, we further calculated the Z'-score difference between sunitinib and sorafenib towards all the proteins, in order to search for the targets with higher affinity (i.e., lower Z'-score) to sunitinib. Then, we performed permutations for each target by randomly selecting two Z'-scores of sunitinib and sorafenib and measuring their difference 10,000 times. Finally, a p-value was obtained as the one-tailed probability when the random values were lower than the difference between sunitinib and sorafenib (see Methods).
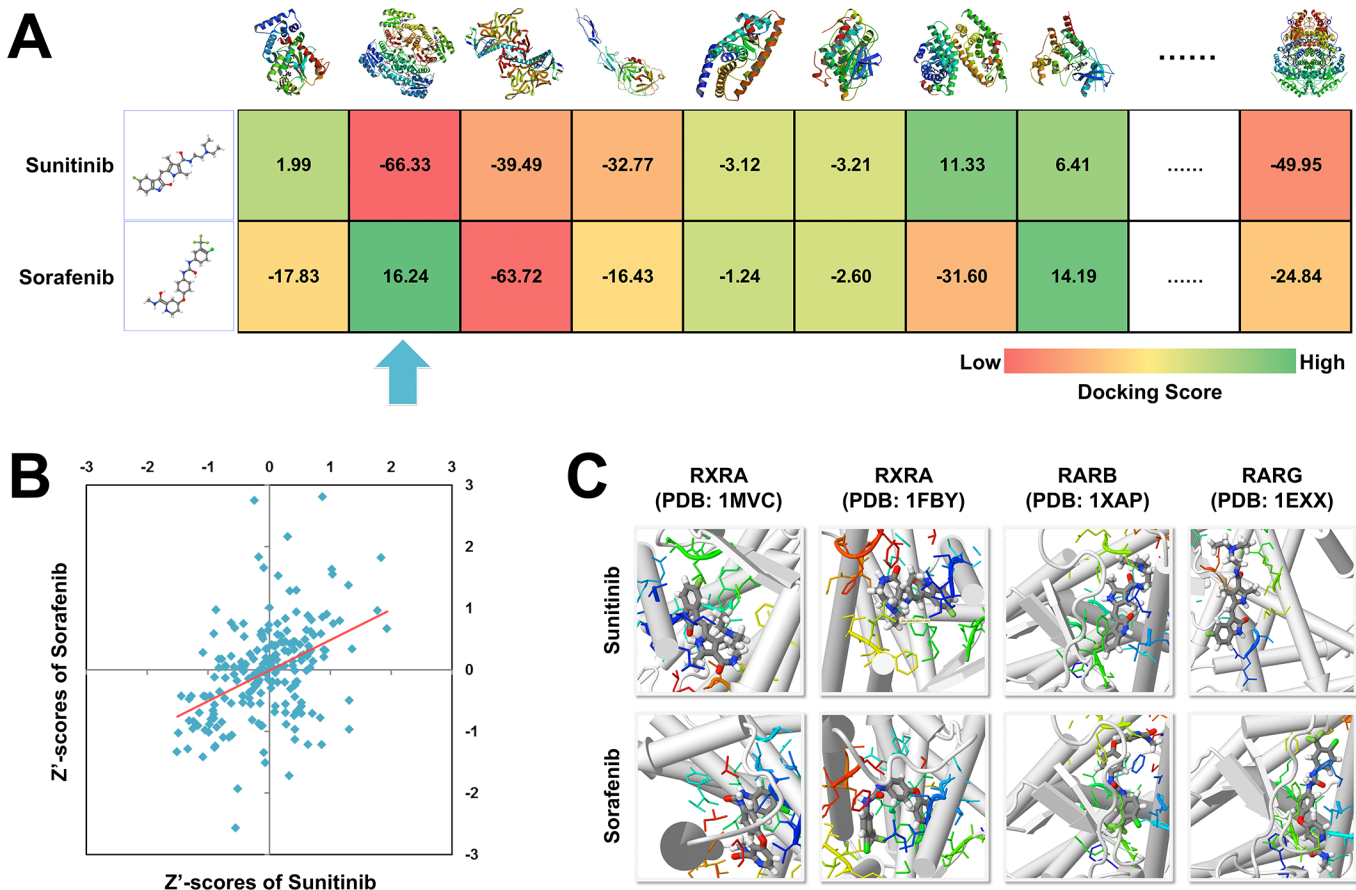
Fig 1. Structural comparison of sunitinib and sorafenib towards potential off-targets. (A) The rationale of the comparison between sunitinib and sorafenib. Simulated binding affinity is measured by docking scores. We pay particular attention to those targets (as indicated by the arrow) showing much higher affinity with sunitinib than with sorafenib. (B) The comparability between sunitinib and sorafenib is verified by their positively correlated Z'-score vectors. (C) The whole molecule of sunitinib binds deep into the pockets of retinoic acid receptors (RXRA has two structure models in Protein Data Bank for docking, while RARB and RARG have one). In contrast, the sorafenib molecule is less well accommodated in the pockets due to steric hindrance in different directions. As suggested by docking scores, the binding strengths of sunitinib towards retinoic acid receptors tend to be higher than those of sorafenib. The figures are produced by DRAR-CPI server.

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Targets with permutation p-value less than the 0.05 cutoff are shown in Table 4, among which the retinoic acid receptors, including retinoic acid receptor RXR-alpha (RXRA), retinoic acid receptor beta (RARB) and retinoic acid receptor gamma (RARG), raise our particular attention. Thyroid hormone activates thyroid hormone receptors, a type of nuclear receptor, which further regulate gene expression by binding to hormone response elements (HREs) in DNA either as monomers, homodimers or heterodimer with other nuclear proteins [25]. It has been repeatedly reported that retinoic acid receptors, in particular, serve as actively hetero-dimer partners for thyroid hormone receptors [26–28]. Showing significantly lower docking Z'-scores towards sunitinib than sorafenib, the retinoic acid receptors specifically provide sunitinib with pockets to deeply fit in (Fig 1C). Given such differences, we hypothesize that sunitinib may profoundly interfere in the function of retinoic acid receptors and disturb thyroid hormone signals (as discussed bellowed).

Table 4. Targets with significantly lower docking Z'-scores towards sunitinib than sorafenib.

PDB ID	Putative Target	Sunitinib Z'-Score	Sorafenib Z'-Score	Difference	P-value
1XAP	Retinoic acid receptor beta	-0.237588	2.74816	-2.985748	0.0041
1MVC	Retinoic acid receptor RXR-alpha	-0.171023	1.83455	-2.005573	0.0293
1EXX	Retinoic acid receptor gamma	0.883029	2.81209	-1.929061	0.0324
1RFN	Coagulation factor IX	0.309693	2.16421	-1.854517	0.0383
1Z6J	Coagulation factor VII	-0.867828	0.979206	-1.847034	0.0388
1FBY	Retinoic acid receptor RXR-alpha	-0.0783559	1.6608	-1.7391559	0.0478

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Discussion

Advances in our understanding of cancer biology lead to the development and approval of various TKI anticancer drugs, such as sunitinib than sorafenib. In the meantime, large-scale data regarding potential safety liability remain rare, but urgently needed to offer alternative treatments to specific patient groups when adverse effect seems unfavorable and intolerable. In particular cases, hypothyroidism refers to a common disease of the endocrine system, which may be caused by low iodine diet [29], autoimmune effects [30] and other factors. Hypothyroidism, as a drug side effect, is uncommonly complicated, because drugs may interfere at different steps in thyroid hormone homeostasis [31,32], including synthesis and secretion from the thyroid gland, thyroid hormone metabolism, absorption of thyroid hormone (especially in patients subject to pre-existed hypothyroidism), etc. While drug induced hypothyroidism is not observed in clinical trials very often, in several independent studies with relatively small samples, unexpected high frequencies of hypothyroidism are found among patients accepting sunitinib treatment [33–36]. This observation gives us strong incentive to confirm the thyroid effect of sunitinib with clinical data in larger scale. More importantly, from the perspective of drug off-targets, we intend to provide an innovative solution to addressing the complexity of thyroid dysfunction and understanding the toxicological mechanisms of sunitinib.

Currently, clinical trials through phase I to III remain the major checkpoints for detecting and preventing potential adverse drug reactions. However, because of the limited number of patients involved and the short duration of the study, some drugs with certain safety liabilities may still be overlooked and approved for marketing [37,38]. Thus, post-marketing pharmacovigilance that begins when the drug enters the general market can play a significant role in early identification and retrospective investigation of overlooked adverse drug events. In the present study, we realized that the large-scale clinical reports documented in FAERS could provide a unique opportunity to consolidate the suspected difference in thyroid toxicity between sunitinib and sorafenib. In addition, despite of the potential complications of sex factor, the higher reporting frequency of hypothyroidism among patients using sunitinib than those using sorafenib proved to be sex-independent. Despite the great value of FAERS data, there are some limitations inherent to its spontaneous nature. For example, all reports in FAERS are related to drug users affected by certain side effects, without healthy or unaffected people as control subjects. Thus, rather than using control subjects, we alternative defined sorafenib as a 'reference drug', which was directly compared with sunitinib (as the 'case drug'). In this way, the problem caused by the lack of control was at least partly avoided. Also, it is important to better understand the safety risks of the combination thyroid cancer therapy. Unfortunately, the number of adverse event reports involving multiple drugs in FAERS data was too low to achieve an acceptable statistical power. Therefore, we suggest that other clinical data regarding the combined treatment should be scrutinized to address this issue. But it should be noted that, although the

FDA's adverse events data were used for this study, the results and conclusions of this article were solely those of the authors and should not represent the opinions of FDA.

By now, several hypotheses have been proposed to explain TKI-induced hypothyroidism, including reduced synthesis of thyroid hormones [33], inhibition of thyroid uptake of iodine [39], atrophy of the thyroid owing to drug toxicity [36], preceding thyroiditis with associated transient thyrotoxicosis [40], and immune dysregulation [41]. However, these theories have yet to be confirmed. More importantly, the mechanism responsible for the development of hypothyroidism in patients treated with sunitinib is still not clearly explained [42,43], suggesting that there can be some previously unknown mechanism of thyroid toxicity. We therefore use DRAR-CPI to explore the potential off-targets for sunitinib. A unique opportunity to addressing this issue is the pharmacological reference provided by sorafenib. According to the guilt-by-association principle, since sunitinib and sorafenib are largely similar in therapeutic effects, their difference in off-target binding may be directly correlated to the hypothyroidism side effect specific to sunitinib. Interestingly, retinoic acid receptors seem to be more probably to interact with sunitinib than with sorafenib. Based on this observation, we propose the following hypothesis. It is well known that thyroid hormone action is mediated by the heterodimers of nuclear thyroid hormone receptors and retinoid acid receptors [27]. Sunitinib may compete with thyroid hormone receptors for the opportunity of binding with retinoic acid receptors, thus deteriorating the dysregulation of thyroid hormone due to either carcinogenesis [44] or radiation therapy [45]. The off-target hypothesis generated in this study can represent candidates for wet-lab toxicological research and biomarker development at genotype and gene expression level in TIK therapy. However, it must be kept in mind that the 208 drug targets covered by DRAR-CPI are only a limited representation of the entire human proteome, leaving numerous targets currently unexamined. Because of that, we expect the CPI servers and other docking tools to evolve and support systematical study on more off-targets in the future.

Despite the progress shown in this study, we believe some improvements and extensions will be necessary and important to better understanding TKI-induced thyroid disorders. First, after binding with protein targets, drug molecules must disturb the expression of certain genes to produce either desirable or unwanted responses. Here we have explored the information about target binding and clinical responses, but in subsequent studies, drug-related genomic expression data at mRNA [46], microRNA [47], metabolic [48] or network [49,50] level should also be examined, so as to further identify the signal pathways involved in hypothyroidism side effect. Second, to further understand drug toxicity at the personalized level, we would explore how the mutations of relevant genes may affect the drug-target interaction [51]. Third, it has been reported by FDA that a higher dose should be a risk factor for drug-induced adverse reactions [52]. However, dosage information was missing in many FAERS reports, which prevented us to examine this aspect in the present study. So we suggest that the dosage factor should be taken into consideration in the subsequent clinical studies on TKIs, so as to further optimize the anti-cancer regimens. Fourth, impact of hypothyroidism (in terms of incidence and grade) may vary between different types of cancer, but this issue was not addressed in the presents study. The current results can warrant subsequent research on the confounding effect of different cancer pathologies. Fifth, besides sunitinib and sorafenib, various TKI drugs are currently used to treat cancer and may cause thyroid reactions. For instance, it has been reported that axitinib may induce thyroid dysfunction in clinical trials [53,54]. Therefore, we expect to apply our method to the adverse effects of axitinib and other TKIs in the future.

In summary, this study presented a practical and efficient strategy of investigating the underlying mechanisms of adverse drug reactions. Due to the complicated nature of *in vivo* drug action, there is usually no initial clue about the reasons of drug toxicity. Fortunately, there are many classes of drugs developed based on the same theory and showing highly similar

pharmacological properties. If empirical observations suggest potential differences in adverse reactions between a test drug of interest and an analogous drug, the procedures demonstrated in this study will illuminate the toxicological mechanisms by, 1) helping confirm the difference in clinical toxicology between the test drug and the analogous drug; 2) predicting the off-target interaction specific to the test drugs. We believe this data-driven strategy would largely enhance the current experiment-based framework of toxicological research.

Materials and Methods

Statistical analysis of drug adverse events

The original reports were restored in the FDA Adverse Event Reporting System (FAERS) and queried through OpenFDA platform following the official tutorial (https://open.fda.gov/api/reference/). The events bearing either sunitinib or sorafenib and submitted from January 2004 to June 2014 were retrieved with the drug generic name "SUNITINIB MALATE" or "SORAFE-NIB". However, the cases that related with both sunitinib and sorafenib were excluded. And for sex-specific analysis, those reports without patient sex information were not counted. With regard to the numbers of hypothyroidism events co-occurred with sunitinib (N_{11}), non-hypothyroidism events co-occurred with sunitinib (N_{10}), hypothyroidism events co-occurred with sorafenib (N_{01}), non-hypothyroidism events co-occurred with sorafenib (N_{00}), we calculated the odds ratio as ($N_{11} \times N_{00}$)/ ($N_{10} \times N_{01}$), in order to examine the difference in the frequency of hypothyroidism reporting. And one-tailed Fisher's exact test was performed to measure the significance level.

Drug-protein docking

The chemical structures of sunitinib and sorafenib, as described by simplified molecular-input line-entry system (SMILES), were queried from the DrugBank database (http://www.drugbank.ca/) and input into the DRAR-CPI online server (http://cpi.bio-x.cn/drar/). Then DRAR-CPI constructed the *in silico* interaction between sunitinib or sorafenib and 208 protein pockets using the Docking method. DRAR-CPI automatically normalized the output Docking scores into Z'-scores, which were exported for subsequent analysis. We calculated the Z'-score difference between sunitinib and sorafenib towards protein i,

$$D_i^{Sun-Sor} = Z'_{i,Sun} - Z'_{i,Sor} \tag{1}$$

We also calculated the probability of the Z'-score difference lower than $D_i^{Sun-Sor}$ regarding two randomly selected proteins among all the 208 targets, which could be expressed as,

$$p_i = P(Z'_{j,Sun} - Z'_{k,Sor} < D_i^{Sun-Sor}) \qquad (j, k \in [1, 208]) \tag{2}$$

The targets with $p_i < 0.05$ were highlighted.

Supporting Information

S1 Dataset. Docking scores of sunitinib and sorafenib towards 208 protein pockets. (XLSX)

Acknowledgments

Author Contributions

Conceived and designed the experiments: MS ZL. Performed the experiments: MS. Analyzed the data: MS. Contributed reagents/materials/analysis tools: MS. Wrote the paper: MS XZ RW ZL BZ.

References

1. Arora A, Scholar EM (2005) Role of tyrosine kinase inhibitors in cancer therapy. J Pharmacol Exp Ther 315: 971–979. PMID: 16002463

2. Yamamoto K, Mizumoto A, Nishimura K, Uda A, Mukai A, et al. (2014) Association of toxicity of sorafenib and sunitinib for human keratinocytes with inhibition of signal transduction and activator of transcription 3 (STAT3). PLoS One 9: e102110. doi: 10.1371/journal.pone.0102110 PMID: 25013907

3. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, et al. (2007) Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 356: 125–134. PMID: 17215530

4. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, et al. (2007) Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 356: 115–124. PMID: 17215529

5. Wilhelm SM, Adnane L, Newell P, Villanueva A, Llovet JM, et al. (2008) Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. Mol Cancer Ther 7: 3129–3140. doi: 10.1158/1535-7163.MCT-08-0013 PMID: 18852116

6. Papaetis GS, Syrigos KN (2009) Sunitinib: a multitargeted receptor tyrosine kinase inhibitor in the era of molecular cancer therapies. BioDrugs 23: 377–389. doi: 10.2165/11318860-000000000-00000 PMID: 19894779

7. Hartmann JT, Haap M, Kopp HG, Lipp HP (2009) Tyrosine kinase inhibitors—a review on pharmacology, metabolism and side effects. Curr Drug Metab 10: 470–481. PMID: 19689244

8. Torino F, Corsello SM, Longo R, Barnabei A, Gasparini G (2009) Hypothyroidism related to tyrosine kinase inhibitors: an emerging toxic effect of targeted therapy. Nat Rev Clin Oncol 6: 219–228. doi: 10.1038/nrclinonc.2009.4 PMID: 19333228

9. Riesenbeck LM, Bierer S, Hoffmeister I, Kopke T, Papavassilis P, et al. (2011) Hypothyroidism correlates with a better prognosis in metastatic renal cancer patients treated with sorafenib or sunitinib. World J Urol 29: 807–813. doi: 10.1007/s00345-010-0627-2 PMID: 21153827

10. Ahmadieh H, Salti I (2013) Tyrosine kinase inhibitors induced thyroid dysfunction: a review of its incidence, pathophysiology, clinical relevance, and treatment. Biomed Res Int 2013: 725410. doi: 10.1155/2013/725410 PMID: 24282820

11. Schmidinger M, Vogl UM, Bojic M, Lamm W, Heinzl H, et al. (2011) Hypothyroidism in patients with renal cell carcinoma: blessing or curse? Cancer 117: 534–544. doi: 10.1002/cncr.25422 PMID: 20845482

12. Yang L, Wang K, Chen J, Jegga AG, Luo H, et al. (2011) Exploring off-targets and off-systems for adverse drug reactions via chemical-protein interactome—clozapine-induced agranulocytosis as a case study. Plos Computational Biology 7: e1002016. doi: 10.1371/journal.pcbi.1002016 PMID: 21483481

13. Omar MA, Wilson JP (2002) FDA adverse event reports on statin-associated rhabdomyolysis. Ann Pharmacother 36: 288–295. PMID: 11847951

14. Piccinni C, Motola D, Marchesini G, Poluzzi E (2011) Assessing the association of pioglitazone use and bladder cancer through drug adverse event reporting. Diabetes Care 34: 1369–1371. doi: 10.2337/dc10-2412 PMID: 21515844

15. Luo H, Chen J, Shi L, Mikailov M, Zhu H, et al. (2011) DRAR-CPI: a server for identifying drug repositioning potential and adverse drug reactions via the chemical-protein interactome. Nucleic Acids Res 39: W492–498. doi: 10.1093/nar/gkr299 PMID: 21558322

16. Bauer M, Glenn T, Pilhatsch M, Pfennig A, Whybrow PC (2014) Gender differences in thyroid system function: relevance to bipolar disorder and its treatment. Bipolar Disord 16: 58–71. doi: 10.1111/bdi.12150 PMID: 24245529

17. Morganti S, Ceda GP, Saccani M, Milli B, Ugolotti D, et al. (2005) Thyroid disease in the elderly: sex-related differences in clinical expression. J Endocrinol Invest 28: 101–104. PMID: 16760635

18. Rezaeian S, Moghimbeigi A, Esmailnasab N (2014) Gender differences in risk factors of congenital hypothyroidism: an interaction hypothesis examination. Int J Endocrinol Metab 12: e13946. doi: 10.5812/ijem.13946 PMID: 24790630

19. Parks JS, Lin M, Grosse SD, Hinton CF, Drummond-Borg M, et al. (2010) The impact of transient hypo-thyroidism on the increasing rate of congenital hypothyroidism in the United States. Pediatrics 125 Suppl 2: S54–63. doi: 10.1542/peds.2009-1975F PMID: 20435718

20. Luboshitzky R, Oberman AS, Kaufman N, Reichman N, Flatau E (1996) Prevalence of cognitive dys-function and hypothyroidism in an elderly community population. Isr J Med Sci 32: 60–65. PMID: 8550351

21. Yang L, Wang KJ, Wang LS, Jegga AG, Qin SY, et al. (2011) Chemical-protein interactome and its application in off-target identification. Interdiscip Sci 3: 22–30. doi: 10.1007/s12539-011-0051-8 PMID: 21369884

22. Yang L, Chen J, Shi L, Hudock MP, Wang K, et al. (2010) Identifying unexpected therapeutic targets via chemical-protein interactome. PLoS One 5: e9568. doi: 10.1371/journal.pone.0009568 PMID: 20221449

23. Law V, Knox C, Djoumbou Y, Jewison T, Guo AC, et al. (2014) DrugBank 4.0: shedding new light on drug metabolism. Nucleic Acids Res 42: D1091–1097. doi: 10.1093/nar/gkt1068 PMID: 24203711

24. Yang L, Luo H, Chen J, Xing Q, He L (2009) SePreSA: a server for the prediction of populations suscep-tible to serious adverse drug reactions implementing the methodology of a chemical-protein interac-tome. Nucleic Acids Res 37: W406–412. doi: 10.1093/nar/gkp312 PMID: 19417066

25. Flamant F, Baxter JD, Forrest D, Refetoff S, Samuels H, et al. (2006) International Union of Pharmacol-ogy. LIX. The pharmacology and classification of the nuclear receptor superfamily: thyroid hormone receptors. Pharmacol Rev 58: 705–711. PMID: 17132849

26. Lee S, Privalsky ML (2005) Heterodimers of retinoic acid receptors and thyroid hormone receptors dis-play unique combinatorial regulatory properties. Mol Endocrinol 19: 863–878. PMID: 15650024

27. Kliewer SA, Umesono K, Mangelsdorf DJ, Evans RM (1992) Retinoid X receptor interacts with nuclear receptors in retinoic acid, thyroid hormone and vitamin D3 signalling. Nature 355: 446–449. PMID: 1310351

28. Berrodin TJ, Marks MS, Ozato K, Linney E, Lazar MA (1992) Heterodimerization among thyroid hor-mone receptor, retinoic acid receptor, retinoid X receptor, chicken ovalbumin upstream promoter tran-scription factor, and an endogenous liver protein. Mol Endocrinol 6: 1468–1478. PMID: 1331778

29. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, et al. (2012) Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid 22: 1200–1235. doi: 10.1089/thy.2012.0205 PMID: 22954017

30. Hadj-Kacem H, Rebuffat S, Mnif-Feki M, Belguith-Maalej S, Ayadi H, et al. (2009) Autoimmune thyroid diseases: genetic susceptibility of thyroid-specific genes and thyroid autoantigens contributions. Int J Immunogenet 36: 85–96. doi: 10.1111/j.1744-313X.2009.00830.x PMID: 19284442

31. Haugen BR (2009) Drugs that suppress TSH or cause central hypothyroidism. Best Pract Res Clin Endocrinol Metab 23: 793–800. doi: 10.1016/j.beem.2009.08.003 PMID: 19942154

32. Surks MI, Sievert R (1995) Drugs and thyroid function. N Engl J Med 333: 1688–1694. PMID: 7477223

33. Wong E, Rosen LS, Mulay M, Vanvugt A, Dinolfo M, et al. (2007) Sunitinib induces hypothyroidism in advanced cancer patients and may inhibit thyroid peroxidase activity. Thyroid 17: 351–355. PMID: 17465866

34. Wolter P, Stefan C, Decallonne B, Dumez H, Bex M, et al. (2008) The clinical implications of sunitinib-induced hypothyroidism: a prospective evaluation. Br J Cancer 99: 448–454. doi: 10.1038/sj.bjc.6604497 PMID: 18665181

35. Rini BI, Tamaskar I, Shaheen P, Salas R, Garcia J, et al. (2007) Hypothyroidism in patients with meta-static renal cell carcinoma treated with sunitinib. J Natl Cancer Inst 99: 81–83. PMID: 17202116

36. Desai J, Yassa L, Marqusee E, George S, Frates MC, et al. (2006) Hypothyroidism after sunitinib treat-ment for patients with gastrointestinal stromal tumors. Ann Intern Med 145: 660–664. PMID: 17088579

37. Wang K, Weng Z, Sun L, Sun J, Zhou SF, et al. (2015) Systematic drug safety evaluation based on pub-lic genomic expression (Connectivity Map) data: myocardial and infectious adverse reactions as appli-cation cases. Biochem Biophys Res Commun 457: 249–255. doi: 10.1016/j.bbrc.2014.12.096 PMID: 25576362

38. Yang L, Wang K, He L (2013) Drug Label Indexing and Mining for Drug Repurposing. Journal of Fudan University (Natural Science) 2013: 6.

39. Mannavola D, Coco P, Vannucchi G, Bertuelli R, Carletto M, et al. (2007) A novel tyrosine-kinase selec-tive inhibitor, sunitinib, induces transient hypothyroidism by blocking iodine uptake. J Clin Endocrinol Metab 92: 3531–3534. PMID: 17595247

40. Grossmann M, Premaratne E, Desai J, Davis ID (2008) Thyrotoxicosis during sunitinib treatment for renal cell carcinoma. Clin Endocrinol (Oxf) 69: 669–672.

41. Ozao-Choy J, Ma G, Kao J, Wang GX, Meseck M, et al. (2009) The novel role of tyrosine kinase inhibitor in the reversal of immune suppression and modulation of tumor microenvironment for immune-based cancer therapies. Cancer Res 69: 2514–2522. doi: 10.1158/0008-5472.CAN-08-4709 PMID: 19276342

42. Torino F, Corsello SM, Longo R, Barnabei A, Gasparini G (2009) Is hypothyroidism a clinically relevant toxicity of tyrosine kinase inhibitors? Thyroid 19: 539–540. doi: 10.1089/thy.2008.0367 PMID: 19416001

43. Surks MI, Hollowell JG (2007) Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab 92: 4575–4582. PMID: 17911171

44. Huang SC, Wu VC, Lin SY, Sheu WH, Song YM, et al. (2009) Factors related to clinical hypothyroid severity in thyroid cancer patients after thyroid hormone withdrawal. Thyroid 19: 13–20. doi: 10.1089/thy.2008.0002 PMID: 19072673

45. Boomsma MJ, Bijl HP, Langendijk JA (2011) Radiation-induced hypothyroidism in head and neck cancer patients: a systematic review. Radiother Oncol 99: 1–5. doi: 10.1016/j.radonc.2011.03.002 PMID: 21459468

46. Wang K, Sun J, Zhou S, Wan C, Qin S, et al. (2013) Prediction of drug-target interactions for drug repositioning only based on genomic expression similarity. Plos Computational Biology 9: e1003315. doi: 10.1371/journal.pcbi.1003315 PMID: 24244130

47. Li Z, Qin T, Wang K, Hackenberg M, Yan J, et al. (2015) Integrated microRNA, mRNA, and protein expression profiling reveals microRNA regulatory networks in rat kidney treated with a carcinogenic dose of aristolochic acid. BMC Genomics 16: 365. doi: 10.1186/s12864-015-1516-2 PMID: 25952319

48. Sun L, Li J, Zhou K, Zhang M, Yang J, et al. (2013) Metabolomic analysis reveals metabolic disturbance in the cortex and hippocampus of subchronic MK-801 treated rats. PLoS One 8: e60598. doi: 10.1371/journal.pone.0060598 PMID: 23577129

49. Chen H, Fang Y, Zhu H, Li S, Wang T, et al. (2014) Protein-protein interaction analysis of distinct molecular pathways in two subtypes of colorectal carcinoma. Mol Med Rep 10: 2868–2874. doi: 10.3892/mmr.2014.2585 PMID: 25242495

50. Zhang B, Wang X, Li S (2013) An Integrative Platform of TCM Network Pharmacology and Its Application on a Herbal Formula, Qing-Luo-Yin. Evid Based Complement Alternat Med 2013: 456747. doi: 10.1155/2013/456747 PMID: 23653662

51. Ganguly D, Chen J (2015) Modulation of the disordered conformational ensembles of the p53 transactivation domain by cancer-associated mutations. Plos Computational Biology 11: e1004247. doi: 10.1371/journal.pcbi.1004247 PMID: 25897952

52. Weng Z, Wang K, Li H, Shi Q (2015) A comprehensive study of the association between drug hepatotoxicity and daily dose, liver metabolism, and lipophilicity using 975 oral medications. Oncotarget 6: 17031–17038. PMID: 26220713

53. Daimon M, Kato T, Kaino W, Takase K, Karasawa S, et al. (2012) Thyroid dysfunction in patients treated with tyrosine kinase inhibitors, sunitinib, sorafenib and axitinib, for metastatic renal cell carcinoma. Jpn J Clin Oncol 42: 742–747. doi: 10.1093/jjco/hys076 PMID: 22628612

54. Fujiwara Y, Kiyota N, Chayahara N, Suzuki A, Umeyama Y, et al. (2012) Management of axitinib (AG-013736)-induced fatigue and thyroid dysfunction, and predictive biomarkers of axitinib exposure: results from phase I studies in Japanese patients. Invest New Drugs 30: 1055–1064. doi: 10.1007/s10637-011-9637-1 PMID: 21301929