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ORIGINAL RESEARCH ARTICLE

Undesirable Effects Related to Oral Antineoplastic Drugs: Comparison Between Patients' Internet Narratives and a National Pharmacovigilance Database

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Abstract

Background The Internet is changing the way people learn about health and illness. Over the previous decade, the oral antineoplastic (OAN) agents have changed patient management allowing more ambulatory care. In this regard, websites could be an interesting source of data about OAN-induced adverse events (AEs).

Objective The aim of the study was to describe the characteristics of AEs, as reported on websites by patients exposed to OAN agents, and to compare these to those recorded in the French pharmacovigilance database (FPVD).

Methods We performed a retrospective study to collect AEs reported by patients in five of the best-known website forums in France over 1 year (2011). For each report, we recorded demographic data, cancer type, drug involved and AEs. The same analysis was done in the FPVD for OAN-induced adverse drug reactions (ADRs).

Results A total of 202 AEs were identified in website posts and 1,448 ADRs were found in the FPVD. The most cited drugs in websites were protein kinase inhibitors ($n = 88$, 43.5 %) and hormone antagonists ($n = 61$, 30.2 %). More musculoskeletal disorder reports were found in the patient websites compared with the FPVD (16.34 vs. 4.70 %, $p < 0.001$). As for skin disorders, we collected fewer reports in the patient website forums than in the FPVD (13.37 vs. 22.17 %, $p = 0.004$). AEs reported in the patient websites were less serious ($n = 10$, 4.95 %) than ADRs recorded in the FPVD ($n = 999$, 68.99 %) ($p < 0.001$).

Conclusions AEs reported in the website forums are considered by patients to be relevant enough to be shared. Data from patient websites could be used as a source of data to detect AEs alongside conventional pharmacovigilance.

Key Points

Patients sharing experiences on a website could be an interesting source of information about drug knowledge and adverse effects

Our data have shown a qualitative difference in the undesirable effects profile for oral antineoplastic agents between spontaneous reports in the French pharmacovigilance database and in patient websites

There is sufficient evidence to re-examine the potential benefits and drawbacks of patient reporting of adverse drug reactions using the Internet, which allows the identification of possible new adverse drug reactions. This type of information should find its place alongside conventional pharmacovigilance

1 Introduction

The Internet is changing the way people learn about health and illness, particularly in chronic diseases such as high blood pressure, diabetes mellitus and heart disease, and is used for information on self-management [1–3]. Health

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sites are among the most popular resources on the Internet [4]. Forums, like other types of social networks, allow individuals to exchange information and experiences but also provide some psychological support. As reported by other authors, patients sharing experiences on a website could be an interesting source of information about drug knowledge and adverse effects (AEs) reported by the patients themselves or by physicians [5, 6]. Patients often look to others who had the same AEs or relate their experiences to other participants in the same situation [7]. Pharmaceutical companies already collect social media postings and analyze them for adverse drug reactions (ADRs) [8]. Chee et al. [9] explored the use of online health forums as a source of data to identify drugs for further scrutiny by the US Food and Drug Administration.

The Internet could be used by survivors of serious diseases to search information on their diagnoses as well as medications and control of ADRs [10, 11]. Regarding antineoplastic agents, Mao et al. [12] suggested that online discussions about aromatase inhibitor-related ADRs were common and often related to drug switching and discontinuation. Benton et al. [13] compared the ADRs of four hormonal breast cancer drugs reported online by patients with those labelled for each drug in the summary of product characteristics. Furthermore, over the last decade, new oral antineoplastic (OAN) agents have changed patient management in oncology allowing more ambulatory care [14]. This mode of administration is more practical, because it does not require the hospitalization of patients. Although doctors warn patients about ADRs before starting treatment with any OAN agent, there remains the issue that some ADRs occur during the therapy for which patients can not systematically ask their doctor about the relationship, the seriousness, the outcome and the necessity of drug withdrawal or dosage modification. In fact, potentially serious ADRs can occur with these drugs, leading to their withdrawal in some cases [15]. In France, a recent study found that antineoplastic agents are the third cause of hospitalization due to ADRs [16]. To our knowledge, a few studies have focused on ADRs induced by OAN agents reported by users in websites. The aim of our study was to describe the characteristics of ADRs reported by patients exposed to OAN agents in online discussions and compare these with those reported by health professionals as recorded in the French pharmacovigilance database (FPVD).

2 Methods

A retrospective study was performed and two sources of data were used: patient websites and the FPVD for the identification and collection of OAN agent-induced ADRs, over 1 year (01/2011–12/2011).

2.1 Selection of Patient Websites

Several French websites were explored and five were selected: Doctissimo, Sante-medecine, E-sante and Aufeminin, because they are the best known and the most visited websites in France for health issues (Uniform Resource Locator is detailed in the flow chart in Fig. 1) [17]. Alte-asso was chosen because of its specificity about questions related to neoplasia. Patient websites were consulted to identify AEs reported by patients throughout their exchange.

Patient narratives reporting OAN-related events were considered as "AEs", and not ADRs, because they were not analyzed by health professionals to assess the causal relationship. In fact, the lack of some data often prevents the application of causality assessment (imputation) method [18].

Contrary to methods performed in other studies using computer-based research to detect drug-induced AEs [12], we undertook a qualitative analysis: all narratives identified by the search engine hosted by each website were independently read by two residents. Table 1 recapitulates the search terms used for the study. We successively analyzed initial threads including at least one OAN-induced AE, and secondary posts related to these threads, also including AEs related to OAN (flow chart in Fig. 1). The labelling of drug(s) involved was done according to the ATC (anatomical therapeutic chemical) classification [19] and AE terms according to the MedDRA® dictionary (medical dictionary for regulatory activities) using system–organ class and preferred terms [20]. Linear-weighted Kappa with 95 % confidence intervals was used to assess the inter-rater reliability. To interpret the level of reliability within the Kappa values, we used the Landis and Koch classification: <0.00, poor; 0.00–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; 0.81–1.00, almost perfect [21]. In this study, a score of 0.61 or higher was considered acceptable.

For each report, we recorded, when available, demographic data about reporters (gender, age) and the family link with the patient concerned with AEs (i.e. the patient him/herself, spouse, parent, child), type of cancer and drug(s) involved classified according to the ATC classification. AEs were analyzed according to MedDRA®. Each narrative was checked 3 months later to add any complementary data (for example, if the suspected drug was withdrawn or not as well as the outcome of the AEs).

For each AE, its seriousness was assessed according to the World Health Organization classification [22]. Moreover, we checked the labelling or not of the reported AE in the European summary of product characteristics [23]. An "unlabelled" ADR is not reported in the summary of product characteristics.

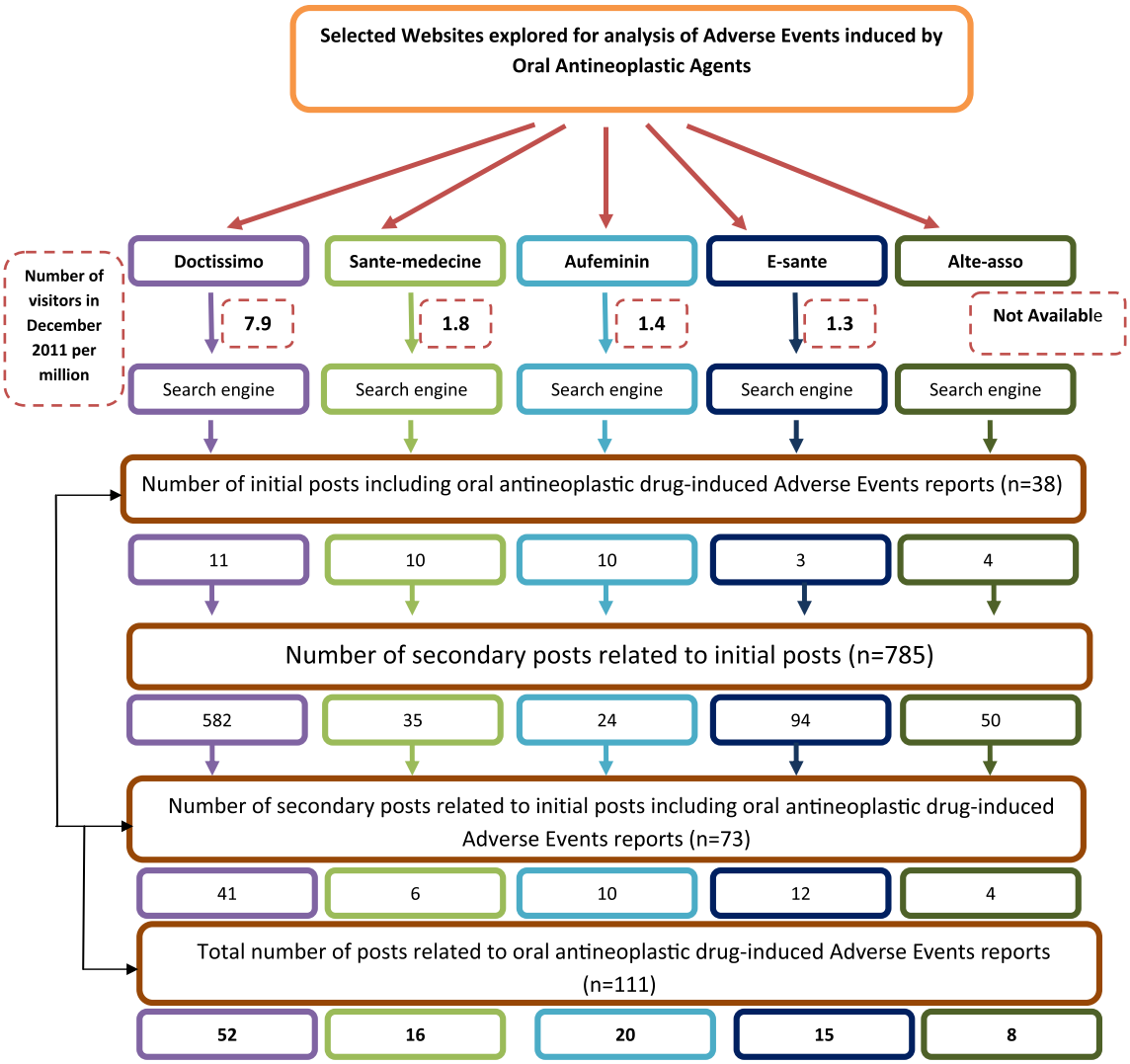

Fig. 1 Flow chart

Table 1 Terms corresponding to oral antineoplastic agents and AEs used for the search engine in each website

Generic terms used for cancer and AEs	Cancer, leucémie, chimiothérapie, orale, effets, réactions, indésirables, secondaires, perturbations
Oral antineoplastic agents available in France (May 2010)	
Alkylating agents	Altretamine (Hexastat®), busulfan (Myleran®), chlorambucil (Chloraminophène®), cyclophosphamide (Endoxan®), estramustine (Estracyt®), lomustine ou CCNU (Belustine®), melphalan (Alkeran®), pipobraman (Vercyte®), procarbazine (Natulan®), témozolomide (Temodal®)
Antimetabolites	Methotrexate (Novatrex®), fludarabine (Fludara®), capecitabine (Xeloda®), tegafur-uracile (UFT®), hydroxycarbamide (Hydrea®), mercaptopurine ou 6-MP (Purinéthol®), thioguanine ou 6-thioguanine (Lanvis®)
Plant alkaloids and other natural products	Vinorelbine (Navelbine®), etoposide (Celltop® and Vepeside®)
Cytotoxic antibiotics and related substances	Idarubicin (Zavedos®)
Protein kinase inhibitors	Dasatinib (Sprycel®), erlonitib (Tarceva®), géfitinib (Iressa®), imatinib (Glivec®), lanatinib (Tyverb®), nilotinib (Tasigna®), sunitinib (Sutent®), sorafenib (Nexavar®)
Differentiating agents	Tretinoin (Vesanoid®), bexarotene (Targretin®)
Other antineoplastic agents	Anagrelide (Xagrid®), diethylstilbestrol (Distilbene®), mitotane (Lysodren®), thalidomide (thalidomide), lenalidomide (Revlimid®)

AEs adverse events

2.2 Data Collection in the French Pharmacovigilance Database

The FPVD consists of a network of 31 regional centres. The FPVD was established in 1985 to record ADRs spontaneously reported by healthcare providers, after validation of data including assessment of causal relationship [24]. At the end of 2011, 438,024 spontaneous reports were recorded in the FPVD. In the French system, until 2011, healthcare providers could only report ADRs. Since 10 June 2011, French law has allowed patients to directly report any ADRs to a pharmacovigilance centre.

Analysis was done on the FPVD for the same period: all cases of ADRs spontaneously reported and registered with OAN agents considered as "suspect" were selected and analyzed. The labelling of drug(s) involved and the ADRs were similar to those of websites using the ATC classification and MedDRA®. Data items recorded were similar for the two sources, the FPVD and patient websites.

Finally, we described and compared the AE or ADR profile of each OAN agent between spontaneous reporting of patient websites and the FPVD. A Pearson's chi-squared test (with Yates' continuity correction when necessary) was performed to compare AEs in forums with ADRs in the FPVD for all OAN agents.

3 Results

The reading of the narratives by two residents allowed the identification of a total of 38 initial threads including at least one OAN-induced AE in the five forums. Second, we found 785 posts corresponding to the initial threads including 73 posts reporting AE with OAN agents (see flow chart). Then, a total of 111 posts (14.14 %) were analyzed. The inter-rater estimated reliability was 0.8 ($p < 0.05$).

These reports concerned 66 Internet users (46 women, 17 men and 3 unknown). The age range was 21–71 years. The relationship between AE reporter and patients are presented in Table 2. Narratives were done mainly by the patient him(her)self. AEs concerned OAN agents mainly used for haematological ($n = 26$, 39.4 %) and breast cancers ($n = 20$, 30.3 %) followed by gastrointestinal tract ($n = 6$), kidney ($n = 4$), liver ($n = 2$), lung ($n = 2$), brain ($n = 1$) and spinal cancers ($n = 1$). In four cases, the type of cancer was unknown.

A total of 202 AEs were identified in websites concerning mainly asthenia (10.89 %) and arthralgia (7.43 %), (corresponding to general disorders and musculoskeletal ADRs), followed by nausea (4.46 %) and decreased appetite (3.96 %). The most commonly cited drugs belonged to two pharmacological classes: protein kinase inhibitors (ATC Class: L01XE) with 88 AEs, and hormone antagonists (ATC Class: L02B) with 61 AEs. AEs led to drug withdrawal in 57 cases, with a decrease of dose in one case. In 118 cases, no modification was done and for 26 cases the outcome remained unknown. Some examples of narratives are summarised in Table 3. The French examples of these narratives are listed in Electronic Supplementary Material 1.

Table 2 Relationship between patient and AE reporter

Patient and AE reporter relationship	Reporter number ($n = 66$), n (%)
Patient him(her)self	47 (71.2)
Spouse/partner	10 (15.2)
Child	4 (6.1)
Brother-in-law/sister-in-law	2 (3.0)
Brother/sister	1 (1.5)
Son-in-law/daughter-in-law	1 (1.5)
Friend	1 (1.5)

AEs adverse events

In the same period, a total of 1,448 ADRs were recorded in the FPVD. The type of reporter (practitioner or lay person) was checked in the FPVD. Given the novelty of the law (allowing patients to report their ADRs), all ADRs were reported by healthcare providers and there was no spontaneous reporting from a patient.

ADRs recorded in the FPVD concerned mainly skin and subcutaneous tissue disorders (22.17 %) and gastrointestinal disorders (15.06 %), followed by general (11.33 %) and respiratory disorders (8.01 %). The drugs most commonly cited belonged to two pharmacological classes: protein kinase inhibitors (ATC Class: L01XE) with 822 ADRs, and hormone antagonists (ATC Class: L02B) with 262 ADRs.

3.1 Comparison of Data Between Adverse Effects (AEs) and Adverse Drug Reactions (ADRs)

3.1.1 Drugs Involved in AEs or ADRs

Table 4 shows the distribution of 17 OAN agents (anagrelide, anastrozole, capecitabine, chlorambucil, dasatinib, erlotinib, everolimus, exemestane, hydroxyurea, imatinib, lenalidomide, letrozole, nilotinib, sorafenib, sunitinib, tamoxifen, temozolomide) according to the ATC classification found in the patient websites and the FPVD.

3.1.2 Repartition of AEs or ADRs

Generally, the comparison between AE and ADR profiles found respectively in patient websites and in the FPVD

Table 3 Examples of patients' narratives regarding oral antineoplastic agents AEs

Categories	Extracts from posts
Reasons for continuing	"For my part, homeopathic treatment improved my bone pains, not completely though, but I'm feeling better"
	"I have eyelids oedemas in the morning when I wake up in the morning. It lasts for a few hours. There might be homeopathy or a cream for this, I'll find out"
Manageable AE	"Proposal of an oral chemotherapy with Nexavar! A weight loss of 24 kg in 11 months, unable to climb stairs, to wipe my feet on a doormat, unable to stand again when I'm squatting, etc. I decided to take care of myself, I forced myself to do cycling everyday, I force myself to walk in the street on a regular basis."
Afraid to stop	"So I wonder if I am not going to stop this poison after those two years. Is there somebody among you who stopped it? If so, did side effects disappear or are they irreversible?"
Benefit outweighs risk	"I have been under glivec 400 mg for 8 years for with a CML, the side effects are for me fatigue, cramp, visual effects, but this is largely bearable compared to the healing effect induced by this molecule, of course in my case but according to my pharmacist, the side effects of glivec are normally bearable."
Reasons for stopping	"Personally, I have been taking this treatment for two and a half years after a treatment with tamoxifen over a period of two years. so I am geting close to the end of the treatment (5 years), however, for about 7–8 months, I feel disorders that are increasing over time (articular pains, increasingly intense fatigue, mood swings, nearing depression) These disorders are disabling. Anyway, I no longer recognize myself. I've been thinking a lot about it and I decided to stop the treatment because I do not see how all this could develop overtime"
Without medical agreement	"Then I very little tolerated the arimidex since I could no longer walk. Tamoxifen gives me fewer side effects but I decided despite medical advice to stop. Today I feel much better but tomorrow?"
With medical agreement	"I am under Aromasin treatment since February 2010, I suffer terribly and I lose my hair, my limbs inflate. My life is like yours, completely wasted, I decided to contact my oncologist tomorrow to change my treatment because I can not stand the constant and daily pain anylonger and it is as hard as with the taxotere [Docetaxel]
	"For me after 6 Xagrid a day, I finally managed to convince the hematologist to move to 5, this is obviously not the best but for me it is better than Hydrea or interferon"
	"With the advice of my oncologist I've just stopped the Aromasin to see if the back pain stops"
Advice	"About Xeloda, one of my acquaintances used to take Xeloda tablets, chemo to do at home, she was treated 3 weeks and then stop for 1 week. The treatment was effective and positive but there was painful side effects, with hand-foot syndrome. We can limit damages by being vigilant. Be confident,nothing is as before but life goes on!"
	"Only you can decide whether or not to resume chemotherapy: Is the risk-benefit ratio worth it? Not sure. What matters is that you are in agreement with yourself"
Health professional attitudes	"Enduring 5 years like that, despite the docs downplaying the drugs effects and saying that those effects come from elsewhere and not from the drugs (Give me a break!) It sometimes seems that even them are bored with our pains, because they don't have the answers!"

AEs adverse events

Table 4 AEs and ADRs reported for OAN agents in patient websites and the FPVD for each anatomical therapeutic chemical classification (fourth level) in 2011

ATC sub-group (fourth level)	AEs of OAN agents in patient websites, *n* (%)	ADRs of OAN agents in the FPVD, *n* (%)
Nitrogen mustard analogues	3 (1.5)	16 (1.1)
Other alkylating agents	8 (4.0)	27 (1.8)
Pyrimidine analogues	3 (1.5)	152 (10.5)
Protein kinase inhibitors	88 (43.5)	822 (56.8)
Other antineoplastic agents	21 (10.4)	58 (4.0)
Anti-estrogens	7 (3.5)	49 (3.4)
Aromatase inhibitors	54 (26.7)	213 (14.7)
Other immunosuppressants	18 (8.9)	111 (7.7)
Total	202	1448

AEs adverse events, *ADRs* adverse drug reactions, *OAN* oral antineoplastic, *FPVD* French pharmacovigilance database, *ATC* anatomical therapeutic chemical

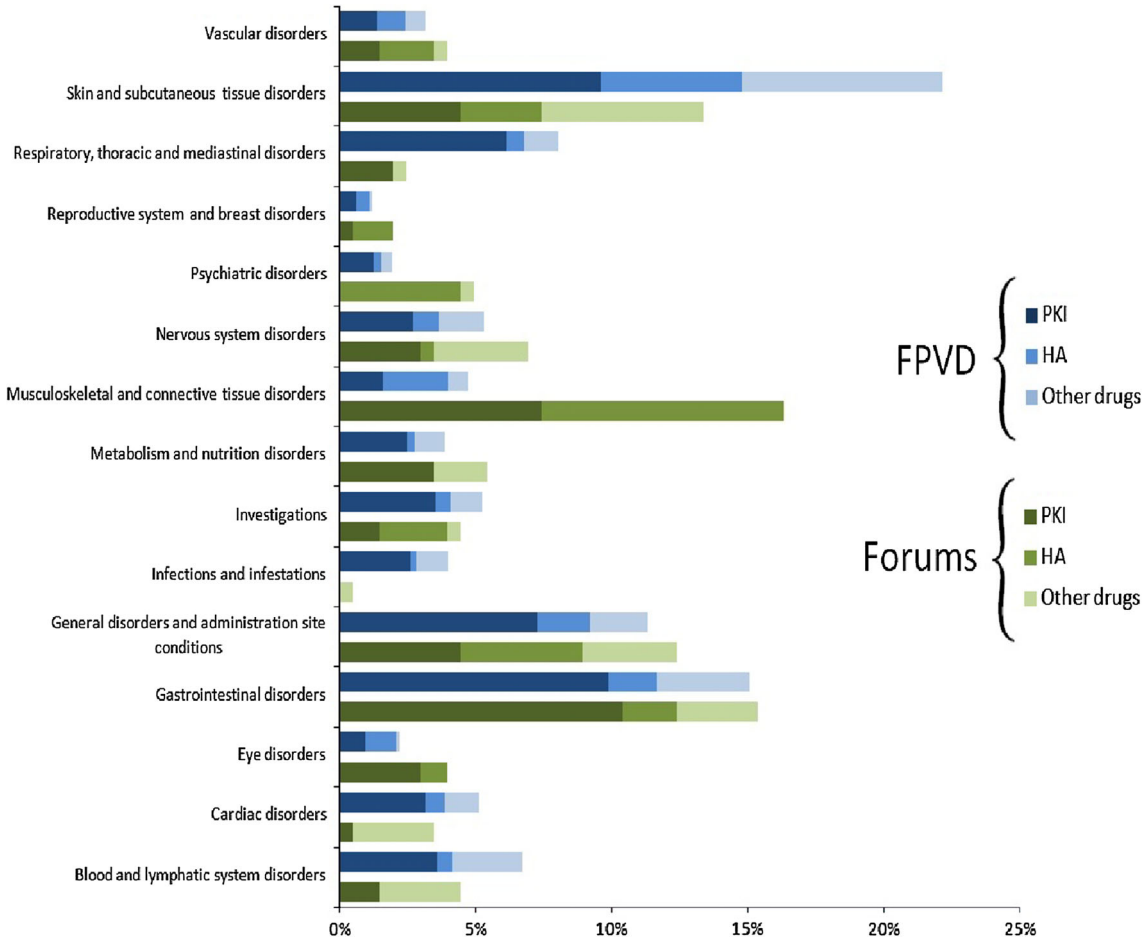

Fig. 2 Frequency of adverse events and adverse drug reactions reported in patient websites and the French pharmacovigilance database (FKPD) for oral antineoplastic agents, protein kinase inhibitors (PKI) and hormone antagonists (HA) (01/2011–12/2011)

(Fig. 2) showed a more frequent reporting of musculoskeletal and connective tissue disorders in website forums (16.34 %) compared with the FPVD (4.70 %) ($p < 0.001$). However, skin and subcutaneous tissue disorders were more reported in the FPVD than in website forums with respectively, 22.17 % and 13.37 % ($p = 0.004$).

For protein kinase inhibitors (dasatinib, erlotinib, everolimus, imatinib, nilotinib, sorafenib, sunitinib), there is no significant difference for skin and subcutaneous tissue disorders between website forums (10.23 %) and the FPVD (16.91 %). However, we found more musculoskeletal disorders in the website forums (17.05 %) than in the FPVD (2.80 %) (with Yates' continuity correction, $p < 0.001$).

For aromatase inhibitors (anastrozole, exemestane, letrozole) and anti-estrogens (tamoxifen), we also found more musculoskeletal disorders in website forums (29.51 %) compared with the FPVD (13.36 %) ($p = 0.002$), whereas skin and subcutaneous tissue disorders were less reported (9.84 %) in patient websites than in the FPVD (28.63 %) ($p = 0.002$).

3.1.3 Characteristics of AEs or ADRs

AEs reported in patient websites were less "serious" [$n = 10$, 4.95 %, mainly related to hospitalization ($n = 8$) or several consultations ($n = 2$)] than those identified in the FPVD ($n = 999$, 68.99 %) ($p < 0.001$). However, in patient websites, 15.84 % of AEs were unlabelled ($n = 32$), of which three were assessed as "serious". Less than half of the unlabelled AEs ($n = 15$) reported in patient websites were found in the FPVD, corresponding to 38 case reports (Table 5).

Details of AEs, ADRs and suspected drugs with the corresponding ATC class are listed in Electronic Supplementary Material 2.

4 Discussion

Our data have shown a difference in the undesirable effects profile for OAN agents between the FPVD and patient websites. This difference must be discussed: first, AEs

Table 5 Unlabelled AEs or ADRs reported in patient websites and the FPVD

OAN agent	Unlabelled AEs (MedDRA® PT)	Seriousness	Number of same ADRs in the FPVD ($n = 38$)
Anagrelide	Chest pain	Non serious	2
Anagrelide	Mitral valve disease	Serious	0
Anastrozole	Dry eye	Non serious	5
Anastrozole	Libido decreased	Non serious	2
Anastrozole	Weight increased	Non serious	5
Chlorambucil	Dizziness	Non serious	1
Chlorambucil	Headache	Non serious	1
Chlorambucil	Petit mal epilepsy	Non serious	0
Erlotinib	Agueusia	Non serious	1
Erlotinib	Gingival pain	Non serious	0
Erlotinib	Haemoptysis	Serious	4
Erlotinib	Toothache	Non serious	0
Everolimus	Hypomagnesaemia	Serious	0
Exemestane	Colitis	Non serious	0
Exemestane	Hand deformity	Non serious	0
Exemestane	Libido decreased	Non serious	0
Exemestane	Memory impairment	Non serious	0
Exemestane	Mood disorder	Non serious	0
Exemestane	Mood disorder	Non serious	0
Exemestane	Weight increased	Non serious	0
Exemestane	Weight increased	Non serious	0
Hydroxycarbamide	Agueusia	Non serious	0
Imatinib	Bone pain	Non serious	4
Imatinib	Osteoporosis	Non serious	1
Imatinib	Pelvic fluid collection	Non serious	0
Imatinib	Tendinitis	Non serious	1
Imatinib	Tooth fracture	Non serious	2
Lenalidomide	Hyperhidrosis	Non serious	1
Letrozole	Dermatitis bullous	Non serious	0
Tamoxifene	Ocular hyperaemia	Non serious	1
Tamoxifene	Weight increased	Non serious	7
Temozolomide	Oesophageal irritation	Non serious	0

AEs adverse events, *ADRs* adverse drug reactions, *FPVD* French pharmacovigilance database, MedDRA® medical dictionary for regulatory activities, *OAN* oral antineoplastic, *PT* preferred term

reported in the patient websites were not significant enough to be taken into account by doctors, who are the main reporters in the pharmacovigilance database and who are more interested in "serious", clinically explicit and less subjective AEs [25, 26]. Second, AEs found in the patient websites were mainly subjective and associated with unpleasant sensations (pain, nausea, asthenia) affecting a patient's quality of life. Our previous data found that doctors report more serious or biological AEs than subjective AEs [27]. Third, patients could establish a causal relationship between their symptoms and a new introduced drug, whereas doctors took into account several medical data (i.e. chronology, semiology, underlying disease, other drugs). In our study, all medical data for patients were not available and the causal relationship was not assessed. This could partly explain the AE profile differences observed between website forums and the FPVD. For protein kinase inhibitors, musculoskeletal disorders are prevalent in website narratives. In fact, skin ADRs are well described with these drugs and often lead to their discontinuation, while musculoskeletal pain is perceived by a health practitioner as less serious and does not need a drug withdrawal [28]. However, in some website forums dealing with hormone antagonists, patients discussed drug benefits after they experienced arthralgia on a daily basis and asked about its discontinuation. These analyses are also suggested by other authors, i.e. the occurrence of AEs could lead to lower compliance [12, 29, 30]. Finally, according to our results, unlabelled ADRs have been identified in the FPVD as well as in social websites. Moreover, about half of the

unlabelled AEs found in patient websites were not described in the FPVD. The difference in the ADR profile was also found for other drugs: Hughes et al. [31] showed that consumer reviews and professional drug descriptions reported similar effects (efficacy or ADRs) for two psychotropic drugs but differed in their descriptions and in the reporting frequency. Hazell et al. [32] investigated the relative contribution of patient reporting of ADRs in the UK's Yellow Card Scheme through disproportionality analysis. They found that a higher proportion of signal disproportionate reporting identified by a healthcare professional involved "serious" ADRs or newly marketed drugs. The proportion of unlabelled AEs was similar in each group.

Our study had some limitations. Contrary to Mao et al. [12], we did not perform a computer-based research study allowing us to analyse more accurately the narratives of patients and to take into account all duplicated reports. This qualitative analysis could improve the understanding of events and choose the better AE term beyond the sometimes misleading simplifications of MedDRA®. However, this led to less statistical power because of less posts analysed. Furthermore, in our study, two cancer types are over-represented (blood and breast cancers), because OAN agents are widely used in these cancers. Consequently, two pharmacological classes labelled for these types of cancers are dominant (protein kinase inhibitors and hormone antagonists). Finally, as cited above, the possibility of recording patients' spontaneous reporting in the FPVD from 2010 could also induce a bias in the analysis of the FPVD according to the reporter. However, taking into account the period of our study, we did not identify any spontaneous reporting from patients for OAN agents in the FPVD. Consequently, we believe the heterogeneity of the reporter is not really a bias for this study.

5 Conclusion

The main finding of the present study is that undesirable effects reported in patient websites and the medical database are qualitatively different, suggesting the interest of their combination. Drug use data extracted from online social media may be a useful tool in pharmacovigilance to understand patients' perceptions of ADRs. In fact, the perception of risk should vary between patient and health professional and the use of a complementary data source should contribute to a better drug profile security assessment [5]. The added value of patient reporting to existing pharmacovigilance systems allows the identification of possible new ADRs [33]. Narratives from patients' websites could be used as a tool to analyse the "social metabolism" of drugs [6, 34]. Currently, there is sufficient evidence to re-examine the potential benefits and drawbacks of patient reporting of ADRs via this simple method of the Internet, as well as the potential effects on reported adherence [35, 36]. This type of information should find its place alongside conventional pharmacovigilance.

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