Case Report

Concomitant Administration of Capecitabine and Folate Supplements: Need to Encourage Medication Reconciliation

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Abstract: Hand-Foot syndrome (HFS) and diarrhoea are dose-limiting Adverse Drug Reactions (ADRs) of capecitabine-based chemotherapy. Four polymorphisms in the dihydropyrimidine dehydrogenase (DPYD) gene, encoding the DPD enzyme responsible for the metabolism of fluoropyrimidines, such as capecitabine, are strongly associated with severe ADRs, and their screening should be performed before starting treatment. Moreover, capecitabine-related toxicity may worsen due to drug-drug and drug-supplement interactions. Here we investigated factors responsible for severe HFS and diarrhoea presented by two patients, non-carriers of the recommended DPYD single nucleotide polymorphisms (SNPs) but carriers of other genetic variants suggested to increase the risk of capecitabine-related ADRs. Through careful therapy recognition, we demonstrated that, unknown to the oncologists, the patients were taking folic acid during the treatment with capecitabine at a dosage higher than 2000 mg/m², which is the maximum tolerated dose when folate is administered. To resolve the ADRs, the therapy had to be drastically changed. In one case, dose reduction of capecitabine and discontinuation of lipid-lowering agents were carried out. In the other case, discontinuation of capecitabine and folic acid and capecitabine re-administration were performed after a month. Genetic and environmental factors should be considered good predictors of severe capecitabine-related toxicity. Medication reconciliation should be encouraged to avoid the harmful consequences of inappropriate treatments.

Keywords: fluoropyrimidines; folic acid; toxicity; adverse drug reactions; hand foot syndrome; diarrhoea

1. Introduction

Fluoropyrimidines (FPs), such as 5-fluorouracil (5-FU) and capecitabine, are anticancer agents widely used to treat several solid tumours [1]. FPs exert their main anticancer effect by inhibiting thymidylate synthase (TS). The strength of this inhibition is increased...
by the presence of folates, which work as essential coenzymes for synthesising nucleic acids [2]. Hand Foot Syndrome (HFS) and diarrhoea are common dose-limiting ADRs of FPs. HFS can involve hands and/or feet with symptoms such as numbness, dysesthesia/paraesthesia, erythema, swelling, blisters, ulceration, desquamation and severe pain [3]. DihydroPyrimidine Dehydrogenase (DPD), encoded by the DPYD gene, is the enzyme involved in the catabolism of more than 80% of FPs. More than 160 single nucleotide polymorphisms (SNPs) have been identified in the DPYD gene, and it is now recommended to perform pharmacogenetic testing to detect four of them before starting FP therapy [4–7]. Specifically, the loss-of-function polymorphisms DPYD c.1905+1G>A and DPYD c.1679T>G almost completely abolish DPD activity, while the variant alleles c.2846A>T and c.1129–5923C>G are correlated with moderate protein loss function [6,7].

It has been reported that up to 50% of patients carrying DPYD SNPs suffer from severe ADRs [8]. However, several patients show FP-related toxicity regardless of the presence of these SNPs, and genetic and nongenetic factors should be considered to prevent even life-threatening ADRs [9,10].

In addition to DPYD SNPs, other polymorphisms in other genes involved in the FP pathway or the metabolism of oncologic drugs frequently co-administered with FPs (e.g., oxaliplatin) may be associated with toxicity occurring during an FP-based treatment. The tandem repeat of a 28–base pair (bp) sequence that is present in either duplicate (2R) or triplicate (3R) in the promoter enhancer region of thymidylate synthase (TS) gene (TSER 2R/3R polymorphism) has been suggested as a predictive biomarker of capecitabine-related toxicity [11,12]. Other involved polymorphisms implicate genes such as 5,10-methylenetetrahydrofolate reductase (MTHFR), cytidine deaminase (CDA), Glutathione S-Transferase-P1 (GSTP1), Excision Repair Cross-Complementation Group 1 (ERCC1) and X-ray Cross-Complementing protein 1 (XRCC1) [13,14].

The toxicity associated with chemotherapy, including a capecitabine-based regimen, may worsen due to drug-drug interactions (DDIs) and/or drug-supplement interactions. However, they are often overlooked [15,16]. Indeed, as stated in the Summary of Product Characteristics (SmPC), the maximum tolerated dose (MTD) of capecitabine is 2000 mg/m² per day when used in combination with folinic acid/leucovorin (LV) or folate supplements.

Medication reconciliation is a valuable process for preventing medication errors, including DDI-related adverse events [17]. However, more than 40% of medication errors are believed to result from inadequate reconciliation, especially during the transition of care. Notably, about 20% of these errors are believed to result in harm [18]. Unfortunately, inappropriate use of dietary supplements is not always recognized, especially since these products are often perceived as beneficial substances with no side effects [19,20].

We have described here the steps of a retrospective analysis conducted to investigate factors responsible for the severe toxicity presented by two patients on capecitabine-based therapy. This analysis highlights the need to encourage medication reconciliation in clinical practice.

2. Results
2.1. Clinical Case of Patient 1
A Caucasian 73-year-old female patient with stage III adenocarcinoma of the right colon had undergone a right hemicolectomy with lymphadenectomy in a University Hospital of Rome. The patient’s medical history included atrial fibrillation and grade II aortic regurgitation. Medications included esomeprazole 20 mg/day, verapamil 40 mg/day, flecainide 100 mg/day, apixaban 2.5 mg/day, ezetimibe 10 mg/day, indapamide 2.5 mg/day and lovastatin 10 mg/day. She was admitted to the University Hospital of Salerno oncology unit to start adjuvant therapy. Based on clinicopathological characteristics and tumour stage, the patient was scheduled for an adjuvant CAPOX chemotherapy regimen consisting of a 2-h intravenous infusion of oxaliplatin (130 mg/m²) on day one and oral capecitabine (1000 mg/m², twice daily) from day 1 to 14, every three weeks. Considering her Body
Surface Area (BSA), the patient assumed 3000 mg of capecitabine daily and 195 mg of oxaliplatin (Table 1).

Table 1. Demographic and clinicopathologic characteristics of patients 1 and 2.

| Characteristics          | Patient 1          | Patient 2          |
|--------------------------|--------------------|--------------------|
| Sex                      | Female             | Female             |
| Age (years)              | 73                 | 85                 |
| BSA (m²)                 | 1.5                | 1.4                |
| Primary tumour site       | Colon/rectum       | Colon              |
| Tumour stage (AJCC TNM)  | III                | IV                 |
| Chemotherapy regimen     | CAPOX (capecitabine) | capcitabine 800 mg/m² BID plus oxaliplatin 130 mg/m² |

Table 2. The table shows the genotypes of patients 1 and 2 based on pharmacogenetic tests performed according to their chemotherapy regimens (CAPOX and capecitabine, respectively). The screening results of the recommended DPYD SNPs (marked with an asterisk) are reported together with those of other polymorphisms proposed as potential predictive factors of FP-related toxicity.

| Polymorphisms | Genotype of Patient 1 | Genotype of Patient 2 |
|---------------|-----------------------|-----------------------|
| DPYD c.1905+1G>A (rs3918290) | GG                    | GG                    |
| DPYD c.1679T>G (rs55886062)    | TT                    | TT                    |
| DPYD c.2846A>T (rs67376798)    | AA                    | AA                    |
Table 2. Cont.

| Polymorphisms                  | Genotype of Patient 1 | Genotype of Patient 2 |
|--------------------------------|-----------------------|-----------------------|
| *DPYD c.1129-5923C>G          | CC                    | CC                    |
| (rs75017182)                  |                       |                       |
| DPYD c.2194G>A                | GG                    | GG                    |
| (rs1801160)                  |                       |                       |
| CDA c.79A>C                   | AA                    | AA                    |
| (rs2072671)                  |                       |                       |
| TSER 2R/3R                   | 2R/2R                 | 2R/2R                 |
| (rs45445694)                 |                       |                       |
| MTHFR c.677C>T               | CC                    | CC                    |
| (rs1801133)                  |                       |                       |
| MTHFR c.1298A>C              | CC                    | AA                    |
| (rs1801131)                  |                       |                       |
| GSTP1 c.313A>G               | AG                    | -                     |
| (rs1659)                     |                       |                       |
| ERCC1 c.*197G>T              | GT                    | -                     |
| (rs3212986)                  |                       |                       |
| ERCC1 c.354T>C               | TC                    | -                     |
| (rs11615)                    |                       |                       |
| XRCC1 c.1196A>G              | GG                    | -                     |
| (rs25487)                    |                       |                       |

Abbreviations: DPYD, dihydropyrimidine dehydrogenase; CDA, cytidine deaminase; TSER, thymidylate synthase enhancer region; MTHFR, methylene-tetrahydrofolate reductase; GSTP1, Glutathione S-Transferase Pi 1; ERCC1, excision repair cross-complementing group 1; XRCC1, X-ray cross complementing protein 1.

2.2. Clinical Case of Patient 2

A Caucasian 85-year-old female was admitted to the University Hospital of Salerno for mild abdominal pain and nausea. The patient’s past medical history included hypertension and mild cognitive impairment. Abdominal ultrasound and CT scan revealed a right ascending colon tumour lesion. The patient underwent a right hemicolectomy with lymphadenectomy. Histological examination demonstrated Stage II colon cancer. The patient was scheduled for clinical and radiological follow-up based on clinicopathological characteristics. After 18 months of follow-up, a whole-body CT scan demonstrated multiple liver metastasis development. In addition, both levels of CEA and CA 19.9 were increased. Molecular analysis of the primary tumour demonstrated no alterations in *BRAF* or *RAS* genes. Due to advanced age and comorbidities, the patient underwent a chemotherapeutic regimen with reduced doses of capecitabine (800 mg/m$^2$) administered on days 1 to 14 every three weeks in monotherapy. Having a BSA of 1.4 m$^2$, she assumed 2240 mg of capecitabine daily (Table 1). Further patient’s medication included iron (319 mg/day), enalapril 10 mg/day and aspirin 100 mg/day. Following 5 cycles of capecitabine, a whole-body CT scan demonstrated a partial response according to RECIST v.1 [22] and normalised serum levels of both CEA and CA 19.9. This response was confirmed on the successive restaging of the disease on capecitabine treatment, and no ADRs were reported. After 15 cycles of capecitabine, according to the CTCAE version 5.0 [21], the patient developed a grade 4 HFS (Figure 1). Only after the occurrence of the severe ADR, the oncologists revealed that the patient, on her own, had started to assume a multivitamin supplementation, including folic acid 400 mcg, iron 21 mg, vitamin C 75 mg and acerola 300 mg concomitantly with capecitabine. Treatment with capecitabine and multivitamin supplementation (comprising folic acid) was discontinued, and appropriate supportive treatment was started. In September 2021, a new CT scan demonstrated a further partial response to the therapy with a decrease in the number and diameter of liver tumour lesions. In addition, a clinical examination of the patient reveals the complete resolution of HFS-related symptoms. As a result, capecitabine treatment was restarted, while folate supplementation was avoided. Following four more cycles of capecitabine, no ADRs were reported. A new CT scan was performed,
demonstrating a progression of the disease with an increase in the number and diameter of tumour liver lesions. Capecitabine treatment was stopped, and a new treatment with trifluridine/tipiracil was started.

Figure 1. Pictures of grade 4 HFS developed by patient 2. The pictures were taken at different times: (a) after 15 cycles of capecitabine when the patient was concomitantly assuming folate supplementation; (b) following discontinuation of capecitabine and folate supplementation; (c) after capecitabine restarting.

As in the case of patient 1, this patient was a non-carrier of the four DPYD SNPs for which screening is recommended but was homozygous for TSER 2R/2R gene polymorphism. The results of all analysed polymorphisms are reported in Table 2.

To assess the potential association of all medicines and supplements to the ADRs, a causality assessment was performed using Naranjo Algorithm (NA). Regarding patient 1, a possible association between the reported ADRs and all medicines was found (Table 3).

Table 3. Causality assessment performed using Naranjo Algorithm for patient 1.

| Diarrhoea Baseline | No Diarrhoea After Therapy Modification | HFS Baseline | No HFS After Therapy Modification |
|--------------------|----------------------------------------|--------------|----------------------------------|
| DRUG               | NA SCORE | DRUG               | NA SCORE | DRUG               | NA SCORE | DRUG               | NA SCORE |
| capecitabine 1000 mg/m², twice daily | 3 | capecitabine 625 mg/m², twice daily (reduction) | 4 | capecitabine 1000 mg/m², twice daily | 3 | capecitabine 625 mg/m², twice daily (reduction) | 4 |
| oxaliplatin 130 mg/m² | 3 | oxaliplatin 100 mg/m² (reduction) | 4 | oxaliplatin 130 mg/m² | 3 | oxaliplatin 100 mg/m² (reduction) | 4 |
| verapamil | 3 | verapamil | 3 | verapamil | 2 | verapamil | 2 |
| flecaïnide | 3 | flecaïnide | 3 | flecaïnide | 2 | flecaïnide | 2 |
| apixaban | 2 | apixaban | 2 | apixaban | 2 | apixaban | 2 |
| indapamide | 2 | indapamide | 2 | indapamide | 2 | indapamide | 2 |
| lovastatin | 3 | lovastatin (dechallange) | 4 | lovastatin | 2 | lovastatin (dechallange) | 3 |
| ezetimibe | 3 | ezetimibe (dechallange) | 4 | ezetimibe | 2 | ezetimibe (dechallange) | 3 |
| Iron, vitamin C, acerola and folic acid, vitamins B | 3 | Iron, vitamin C, acerola and folic acid, vitamins B | 3 | Iron, vitamin C, acerola and folic acid, vitamins B | 2 | Iron, vitamin C, acerola and folic acid, vitamins B | 2 |

Abbreviations: NA, Naranjo Algorithm; HFS, Hand-Foot-Syndrome.
Regarding patient 2, a probable association between HFS and capecitabine was found both at baseline (with an NA score of 6) and after therapy modifications (with an NA score of 7) (Table 4).

Table 4. Causality assessment performed using Naranjo Algorithm for patient 2.

| DRUG                      | NA SCORE | DRUG                      | NASCORE | DRUG                      | NASCORE |
|---------------------------|----------|---------------------------|---------|---------------------------|---------|
| capecitabine              | 800 mg/m², twice daily | 6 | capecitabine              | 800 mg/m², twice daily | 7 |
| folic acid supplement     | 2        | folic acid supplement     | 3       | folic acid supplement     | 3       |
| Iron supplement           | 2        | Iron supplement           | 2       | Iron supplement           | 2       |
| aspirin                   | 2        | aspirin                   | 2       | aspirin                   | 2       |
| enalapril                 | 2        | enalapril                 | 2       | enalapril                 | 2       |

Abbreviations: NA, Naranjo Algorithm; HFS, Hand-Foot-Syndrome.

2.3. Identification of Drug-Drug and Drug-Supplement Interactions

Five drug interaction checkers (Drugs.com, Drugbank, Medscape, WebMD and Lexicomp) were used to identify potential clinically relevant interactions between folate supplementation and capecitabine.

Among the easy-to-use online tools, four of them are available for free, while one (i.e., Lexicomp) requires payment for consultation and contains “evidence-based” drug-drug interaction (DDI) information [24].

Notably, all of the drug interaction checkers used could have identified increased risk of toxicity following the concomitant administration of capecitabine and folate supplements.

In particular, Drugs.com and Drugbank revealed a risk for severe DDI-related ADRs when capecitabine is concomitantly administered with folic acid and/or folinic acid/LV. Medscape and WebMD suggested “monitoring closely” potential DDI between capecitabine and LV, while they did not predict interactions with folic acid. Lexicomp provides a distinction based on the severity of the DDI-related outcomes between capecitabine and folic acid (classified as “major”) or capecitabine and folinic acid/LV (classified as “moderate”).

2.4. Folate/Capecitabine Use: Alert and Mechanism of Interaction

As already discussed, the SmPC of capecitabine states that toxicity may increase when co-administered with associated folinic acid/LV. In particular, the MTD used in combination with folinic acid/LV is 2000 mg/m² per day. The risk of increased capecitabine-related toxicity may also occur with folate supplements because of the similarity between folinic acid/LV and folic acid [25]. The folinic acid/LV is a naturally reduced form of folate, which is easily converted into the active form, tetrahydrofolate (THF), by the methylenetetrahydrofolate dehydrogenase (MTHFD). In contrast, folic acid is the oxidised synthetic form that requires two enzymatic steps to be converted into the active form by the dihydrofolate reductase (DHFR) [25]. Folate is an essential coenzyme for nucleic acid synthesis.

Co-administration with 5-FU and capecitabine determines a pharmacodynamic interaction: FdUMP, one of the 5-FU metabolites, inhibits TS, catalysing the conversion of dUMP in dTMP. FdUMP replaces dUMP and binds to TS in the presence of a reduced form of its natural cofactor (i.e., 5,10-CH2 THF), forming a covalent ternary complex. Notably, the
The strength of this link is directly proportional to the folate concentration. This pathway is illustrated in Figure 2.

**Figure 2.** Folate pathway. Abbreviations: DHFR, Dihydrofolate Reductase; THF, Tetrahydrofolate; MTHFD, Methylenetetrahydrofolate dehydrogenase; 5,10-CH2 THF, 5,10-methylenetetrahydrofolate; 5-CH3 THF, 5-Methylenetetrahydrofolate; CDA, Cytidine Deaminase; 5-FU, 5-fluorouracil; dUMP, deoxyuridine monophosphate; TS, Thymidylate synthase; TSER, thymidylate synthase enhancer region; dTMP, deoxothyridine monophosphate (colour figure).

### 3. Discussion

The clinical cases described here suffered from severe diarrhoea and HFS following concomitant administration of capecitabine and folate supplementation. Both patients took a capecitabine dosage greater than 2000 mg/m² per day, which is the MTD of capecitabine when taking concomitant folate administration [3].

Cancer patients often take vitamin supplements, including those containing folic acid, to make up for any deficiencies in the face of increased metabolic requirements imposed by the tumour [26]. DDIs are one of the most important causes of hospitalization but, are often overlooked due to the absence of a complete patient’s pharmacological anamnesis [15]. This problem is highlighted by the World Health Organization and Regulatory Agencies that encourage the performance of medication reconciliation with careful recognition of all treatments to avoid ADRs caused by medication errors, especially during the transition of care [17-28].

Both clinical cases highlighted the need to encourage medication reconciliation in clinical practice by stimulating patients to report the use of all drugs and dietary supplements.

Patient 1 had undergone a right hemicolectomy with lymphadenectomy at the University Hospital of Rome and she was already taking folic acid before starting, at the University Hospital of Salerno, the adjuvant CAPOX chemotherapy regimen, while patient two had started to take folic acid independently during capecitabine treatment. In both cases, the use of folate supplements was not recorded.

To resolve the severe diarrhoea manifested by patient one, lovastatin and ezetimibe were discontinued, in addition to a reduced dosage of capecitabine and oxaliplatin. This discontinuation proved detrimental to the patient, who suffered from aortic regurgitation and atrial fibrillation. LDL levels increased, exceeding the reference value for a patient at very high cardiovascular risk (i.e., 55 mg/dL) [29]. This underscores the need for therapeutic appropriateness in patients who follow multitherapy due to multiple comorbidities [30-32].

Some studies have suggested that capecitabine toxicity may be increased by previous LV treatment or folate supplements.

Chan et al. conducted a prospective study concerning 144 colorectal cancer patients treated with capecitabine. The authors found grade ≥2 toxicity in nine patients taking folate supplements. The authors found a significant correlation between serum folate levels and toxicity in these subjects, including HFS and diarrhoea [33]. Sharma et al. performed a
phase II study in which the main finding was the occurrence of severe toxicity in patients affected by advanced colorectal cancer who had already undergone an adjuvant FU/LV regimen [34].

Yap et al. suggested that serum and red blood cell folate levels predicted capecitabine-induced HFS ≥ grade 2 [35]. In the RCT named PACT (Patient Preference in Adjuvant Colorectal Therapy) by Hennig et al., an increase in treatment toxicity was reported when patients switched from 5-FU/LV regimen to capecitabine. In this study, pre-treatment with 5-FU 425 mg/m² combined with LV 45 mg once weekly triggered toxicity [36]. Among these four studies, three measured serum folates and all identified a mean value of 16 nmol/L as a cut-off associated with worsened capecitabine-related ADRs [33–35]. Conversely, the study by Alvarez-Cabellos et al., which enrolled only patients treated with 5-FU co-administered with LV, failed to demonstrate a correlation [26]. In this study, patients had a similar degree of toxicity regardless of serum folate levels. In fact, the safety statement reported in the capecitabine SmPC is not present in that of 5-FU.

Both clinical cases described here were not carriers of the DPYD SNPs, for which pharmacogenetic testing is recommended. However, both had the TSER-2R/2R genotype.

The polymorphism TSER 2R/3R is a 28-base pair of short tandem repeats in the TS promoter. As already mentioned, TS catalysed the methylation of dUMP to dTMP, and it is the main target of the FPs [37]. This polymorphism has been associated with capecitabine-related toxicity in patients with advanced colorectal cancer [38,39]. In particular, subjects who are carriers of the TSER-2R/2R genotype could be more likely affected by severe toxicity than those who are carriers of the -3R/3R genotype. This could be related to a decreased TS mRNA expression in the normal tissue of subjects bearing a -3R/3R genotype that may lead to increased TS inhibition by the FP treatment [39,40].

Identifying this polymorphism starting from a peripheral blood sample may be useful in predicting FP-related toxicity, such as HFS and other ADRs, including haematological and gastrointestinal ones [11,41]. Another SNP, referred to as TS c.58G>C (rs2853542) in the sequence of the second repeat of the 3R allele, has been associated with FP-related toxicity [42,43]. However, we did not analyse this SNP in the described clinical cases.

The present study also demonstrated the usefulness of interaction checkers in preventing potentially harmful DDI and emphasised the need to use more than one tool. In fact, all five-interaction checkers consulted suggested and identified the potential of the LV/capecitabine combination to worsen capecitabine-related toxicity, but only three of them (i.e., Drugs.com, Drugbank and Lexicomp) extended this warning to folic acid supplementation. This may lead one to underestimate the risk associated with this form of folate, which has a very similar chemical structure to folic acid [44].

The main limitation of the present study is that it is a case report study involving only two patients; thus, the results cannot be generalized. On the other hand, the evaluation of the clinical cases described here underlines the importance of paying special attention to recognising all medications and supplementations taken by patients, especially during transition care.

4. Materials and Methods

The clinical cases of two patients were followed in an ongoing observational study (Campania Sud Ethics Committee approval n.4_r.p.s.o./2018) at the University Hospital of Salerno “San Giovanni di Dio e Ruggi d’Aragona” were described. This ongoing study integrated clinical monitoring with a pharmacogenetic analysis conducted in patients eligible for FP-based treatment. ADRs are recorded, and their severity is graded according to the Common Terminology Criteria for Adverse Events (CTC-AE) version 5.0. [21]. The Response evaluation criteria in solid tumours (RECIST) v. 1 is used to assess the treatment response [22]. The enrolled patients gave their informed consent to undergo the procedures in the study, the processing of personal data, and the publication of the results.

The screening of DPYD SNPs (c.1905+1G>A, c.1679T>G, c.2846A>T and c.1129–5923C>G) is performed at the Clinical Pharmacology Unit of the University Hos-
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A step-by-step retrospective investigation was performed to assess factors possibly responsible for the severe toxicity in the two clinical cases described here. Naranjo algorithm (NA) was used to evaluate the association between ADRs and patients’ therapy. NA develops an ADR Probability Scale consisting of 10 questions that are answered as either “Yes”, “No”, or “Do not know”. Different point values (−1, 0, +1 or +2) are assigned to each answer. The association drug-ADR is classified as definite, probable, possible, or doubtful. Total scores range from −4 to +13 (definite, score ≥ 9; probable, score 5–8; possible, 1–4; doubtful ≤ 0) [45].

Five drug interaction checkers (Drugs.com, Drugbank, Medscape, WebMD and Lexi-comp) were consulted in this study to identify potential clinical ADRs related to drug-drug and drug-supplement interactions.

Written informed consent was obtained from patient 2 for the publication of Figure 1.

5. Conclusions

Lack of comprehensive recognition of all drugs and supplements taken by patients can generate harmful consequences. This case report study in which two patients were enrolled allowed us to emphasize that medication reconciliation should be encouraged by considering genetic and environmental factors as valid predictors of serious toxicity. This process is necessary for oncology as in other medical areas and requires the involvement of health care professionals, including clinical pharmacologists.

Author Contributions: Conceptualization, B.S., V.C., C.S.; data curation, B.S., C.S., V.C., F.S., E.D.B.; formal analysis, G.C.; investigation, N.B., A.M.P.; methodology, E.D.B., M.T., N.B.; software, G.C.; supervision, V.C., S.P. and A.F.; validation, F.S. and G.C.; writing—original draft, B.S., V.C., C.S., A.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by PROGETTI DI FARMACOVIGILANZA ATTIVA FINANZIABILI ATTRAVERSO I FONDI FV 2012, 2013 e 2014 (Accordo Stato—Regioni—Province Autonome del 30 Marzo 2017).

Data Availability Statement: Data is contained within the article.

Acknowledgments: We thank the native English speaker Jan Festa, who revised the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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