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RESEARCH ARTICLE

Survey of oral chemotherapy safety and adherence practices of hospitals in Spain

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Abstract *Background* Oral chemotherapy is increasingly used for cancer therapy but, without proper practices, creates safety and adherence issues. However, little is known on safety and adherence practices in wide clinical settings. *Objective* To assess the implementation level of safety and adherence practices in oral chemotherapy in Spanish hospitals. *Setting* All Pharmacy services from prescription, dispensation, patient education and monitoring hospitals that prescribe oral chemotherapy of Spain. *Main outcome measure* Level of safety practices regarding oral chemotherapy prescription, dispensation, patient education and adherence. *Method* An 11 multiple-choice-item questionnaire made in consensus with GEDEFO (Spanish Group of Oncology Pharmacists) was sent to all pharmacy services from hospitals that prescribe oral chemotherapy. This questionnaire comprised prescription, dispensation, education and monitoring. We arbitrarily defined three levels of practices: no sufficient specific practices were reported (we termed this as 'level I'); performance of an initial visit with a pharmacist providing written patient educational materials and monitoring adherence (termed as 'level II'); and level II requirements plus electronic chemotherapy ordering system and extra safety practices (termed as 'level III'). *Results* Of the 169 targeted healthcare settings, 86 (50.9 %) responded to the survey. The majority of responding hospitals were public, general, and teaching hospitals with more than 200 beds. Main discrepancies were in electronic prescription of oral chemotherapy and monitoring adherence. There were 32 hospitals (37.2 %) with level I of safety and adherence practices, 38 hospitals (44.2 %) accomplished level II, 16 (18.6 %) hospitals reached level III. No hospital variables were found to be correlated with each level of safety. *Conclusions* The majority of responding hospitals have safety and adherences practices for oral chemotherapy. However, the level of these practices varies. There are significant opportunities for improvement, particularly with regard to electronic prescription of oral chemotherapy and monitoring adherence.

Keywords Administration oral · Antineoplastic agents · Questionnaires · Safety management · Spain

This study was conducted on behalf of GEDEFO group.

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Impact of findings on practice

- In the absence of adequate safety measures, oral chemotherapy could lead to undetected dosing errors.
- There is a need to ensure safe practices and an adequate management of oral chemotherapy by hospital pharmacists in Spain.

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- The heterogeneity of the different implemented safety practices on oral chemotherapy reflects a lack of general consensus in this relatively new field.

Introduction

The use of oral chemotherapy drugs which have been available for decades had been limited by their unpredictable bioavailability and generally drugs given intravenously were preferred. Recently, the introduction of targeted therapy or biological therapy together with the availability of cytotoxic drugs that can be administered by the oral route (e.g., capecitabine, vinorelbine, topotecan) has revolutioned cancer chemotherapy [1]. Currently, oral chemotherapy accounts for 10 % of all chemotherapy treatments and by the end of 2013, this percentage is expected to increase to 25 % [2]. Also, about 50 % of biologics approved for cancer treatment in the European Union since 2000 are only available as oral formulations [3].

In relation to safety issues of oral chemotherapy, a cautious approach is warranted for different reasons, including frequent misunderstanding of fewer side effects, no need of strict control visits as compared with intravenous chemotherapy, or insufficient control at the time of prescribing, dispensing and administering the drugs [2, 4–6]. In the absence of adequate safety measures, dosing errors are possible and may pass undetected [7]. On the other hand, adherence to oral chemotherapy is predicted to be poorer than adherence to chemotherapeutic agents given intravenously [2]. In the setting of hormone therapy in breast cancer patients, poor adherence or early discontinuation of tamoxifen adversely affects survival [8, 9].

Although the need of safety measures and practices in cancer patients treated with oral chemotherapy has been recognized, clinical studies are lacking. There is only a previous survey of US comprehensive cancer centres, in which it was shown that fewer safety standards for oral chemotherapy agents had been adopted as compared with infusion chemotherapy [12]. In addition, there is a lack of international guidelines addressing specifically this issue, so the general recommendation is to follow the same standards as intravenous chemotherapy [10–13]. A need for multidisplicinary approach and continuous processes to improve chemotherapy safety and to reduce medication errors has been highlighted [14] and implies the pharmacists as the key of safety practices to ensure the adequate management of oral chemotherapy [15]. Recently, some recommendations have been published to provide some good practice for the provision of pharmacy services to patients receiving oral chemotherapy [16].

Aim of the study

To assess the implementation level of safety and adherence practices in oral chemotherapy regarding prescription, dispensing, monitoring and patient education in Spain. In this study, the term oral chemotherapy includes the administration of cytotoxic drugs and biologic agents, excluding the use of hormones and corticosteroids.

Methods

Between December 2011 and March 2012, all pharmacy services from hospitals in Spain in which oral chemotherapy for cancer treatment was prescribed were invited to take part in a nationwide survey. In Spain, this medication must be dispensed through a pharmacy service either for cancer or non-cancer indications. For this reason, all hospitals with oral chemotherapy prescription have any kind of pharmacy service. The purpose of which was to collect information on safety measures and practices to ensure adherence to oral cytotoxic drugs in cancer patients. The census of the Spanish Group for the Development of Oncological Pharmacy ("Grupo Español para el Desarrollo de la Farmacia Oncológica", GEDEFO) was used to collect information on all Oncology Pharmacists from all hospitals in Spain. GEDEFO is a consolidated group of hospital pharmacists who work to improve the quality of oncohematological care. A specific questionnaire was developed and sent by e-mail together with a personalized letter explaining the objectives of the study and requesting participation. A second remainder was sent by e-mail 4 weeks later, with a deadline to return the questionnaires on March 31, 2012.

The survey study was approved and supported by GEDEFO. Our hospital ethical committee approved the study.

Description of the questionnaire

A questionnaire was designed and approved by the Executive Committee of GEDEFO, which is composed by nine hospital pharmacists. The content of the questionnaire was discussed in several meetings with members of GEDEFO and was based in part on data of the previously published US survey [17] as well as in our clinical experience in Spain. The questionnaire consisted of 11 multiple-choice items addressing prescription, dispensation, patient education and monitoring with the aim of gathering information on the safety and adherence practices in relation to treatment with oral chemotherapeutic drugs (Electronic Supplementary Material 1). More than one answer for each question was allowed. Moreover, each question had a free-response option in order to avoid constraining responses. In addition, there were several free-response items related to

general characteristics of the hospitals of responders, such as type of dependency (non-profit or private), functional type (general, specialized), teaching hospital (yes, no), and number of beds. Moreover, information on the approximate number of chemotherapy formulations prepared per year was also collected.

Additionally, a general assessment of the implementation of safety practices was performed among respondents. Three levels of safety practices on oral chemotherapy were arbitrarily defined (after validation of the oral chemotherapy prescription) as follows: "level I" when the specific practices did not reach the next level; "level II" when an initial visit with a pharmacist was scheduled (patient education), in which written educational materials were provided and monitoring of adherence; and "level III" that included level II measures and the prescription of oral chemotherapy through an electronic chemotherapy ordering system as well as the implementation of additional safety practices. This arbitrary tool has not been validated.

Definitions

A *paper order form* is defined as the simplest order, either handwritten or printed, indicating only the single oral chemotherapeutic agent to be dispensed. A *printed medical order* form was defined as the order that contains the full medication schedule, including detailing of the full chemotherapy protocol related to the oral chemotherapy agent.

In relation to dispensing, because of the growing number of drugs dispensed exclusively in the hospital setting, an ambulatory care pharmacy practice has emerged. Pharmacists in this decentralized pharmacy model often dispense drugs and attend patients with chronic diseases (HIV infection, hepatitis, rheumatoid arthritis, cancer, etc.) in office visits. The model of hospital pharmacy in Spain has been defined elsewhere [18].

A *pharmacy nurse* was defined as the one involved and specialized in the practice of pharmacy. This is the result of the increasing pharmaceutical services during the last years A 3 year training is required for a pharmacy nurse.

An *initial visit* was defined as the one performed at the first dispensation of the oral chemotherapeutic agent aimed to ensure patient's full understanding of the treatment regimen. GEDEFO triptychs were leaflets with information on oral chemotherapy (supervised by the Spanish Society of Medical Oncology), that briefly describes how each drug works, how it is administered, and identifies information that a patient needs to know to identify, predict, prevent or manage side effects were provided (hand-out materials are available at http://gruposdetrabajo.sefh.es/gedefo/).

Additional safety practices comprised, among others, the double check of the dose prescribed when dosing include calculation (e.g. body surface area).

Statistical analysis

Information collected through the survey was entered into Microsoft Excel (Microsoft Corporation, Redmond, WA), with responses numerically coded and free-text responses transcribed. For questions with an "other" response choice, all responses were reviewed by the investigators in order to ensure the response was conceptually unique and they were classified as another item. Descriptive statistics for each quantitative item were performed. Univariate analyses of hospital variables regarding each level of safety were performed using the χ^2 or Fisher's exact test for categorical variables, and the Student's t test or the Mann–Whitney U test for the continuous variables according to the distribution of data, which was previously assesses with the Kolmogorov–Smirnov test. Predictors of the level of safety practices were assessed using logistic regression models. All variables statistically significant with a P value < 0.20 in the univariate analyses were included in a multivariable logistic regression model. Statistical analyses were performed with the SPSS for Windows, rel. 20.0.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $P < 0.05$.

Results

A total of 86 pharmacy services of the 169 eligible hospitals completed the questionnaire (response rate 50.9 %). All completed surveys were returned from hospitals that prescribed oral chemotherapy. The main characteristics of the participating hospitals are shown in Table 1. Most of them belonged to the public National Health Care Service ($n = 70$, 81.4 %), were acute-care general centers ($n = 82$, 94.2 %), and were university-affiliated institutions ($n = 75$, 87.2 %). Sixty-eight (79.1 %) had more than 200

Table 1 Characteristics of health-care settings

Characteristic	No.	%
Type of dependency		
Non-profit	70	81.4
Private	16	18.6
Functional type		
General	82	94.2
Specialized	4	5.8
Teaching hospital		
Yes	75	87.2
No	11	12.8
Number of beds		
Less than 200	18	20.9
Between 200 and 499	31	36.1
500 or more	37	43.0

beds and 37 (43 %) more than 500. The mean number of intravenous chemotherapy preparations per years 14,594.9 (standard deviation, [SD] 11,658.1, range: 700–50,000; 95 % confident interval [CI] 11,966.4 to 17,223.4).

Prescribing

In almost all cases, oncologists (98.8 %) and haematologists (97.7 %) prescribed oral chemotherapy. However, different specialists other than oncologists or haematologists prescribed oral chemotherapy, such as gastroenterologists in 22.1 % of the hospitals, specialists in internal medicine in 8.1 %, and urologists in 7.0 %, among others (Table 2). In fact, 33 pharmacy services (38.4 %) received prescriptions from more than two services. Oral chemotherapy was ordered mainly using a paper order form similar than order forms used for other outpatient treatment in 80.2 % of the hospitals. Other methods of prescription were electronic chemotherapy ordering system, 36.0 % and printed medical order form, 25.6 %. Two or more methods were indistinctively used in many sites.

Dispensing

In most hospitals ($n = 81$, 94.2 %), oral chemotherapeutic agents were dispensed by the hospital pharmacists (Table 2). Nineteen (33.5 %) pharmacists were fully dedicated to oncology, 39 (48.1 %) were general ambulatory care pharmacist, and 23 (28.4 %) were part-time oncology and part-time general ambulatory care pharmacist. Oral chemotherapeutic agents were also dispensed by nurses, pharmacy technicians, and other personnel. A total of 60.5 % of respondents stated that two or more staff people participated in the dispensing process. Medications were usually dispensed at the hospital pharmacy (89.5 % of cases). Other places included day hospital surgery (12.8 %) or ambulatory care pharmacy (10.5 %). In only two hospitals (2.3 %) there was a specific oncology pharmacy surgery for dispensing.

Patient education

An initial patient education visit was carried on in almost all hospitals (95.3 %) (Table 2) Visits were usually motivated or generated by a prescription of an oral chemotherapeutic drug at the time of dispensing the drug in most hospitals (73.3 %) (Table 2) These visits were commonly performed in the same facilities where the drug was dispensed, including the hospital pharmacy (83.7 %), the day hospital surgery (15.1 %), the ambulatory care pharmacy (9.3 %) or a specific oncology pharmacy surgery (2.3 %). The oncology

Table 2 Results of the questionnaire survey on oral chemotherapy safety and adherence practices of respondent hospitals (86 hospitals)

	N (%) of sites
Prescribing	
1. Medical specialties that prescribe oral chemotherapy*	*86 sites*
1.1. Oncologists	85 (98.8)
1.2. Hematologists	84 (97.7)
1.3. Gastroenterologists	19 (22.1)
1.4. Internists	7 (8.1)
1.5. Urologists	6 (7.0)
1.6. Gynecologists	4 (4.7)
1.7. Pediatrician	4 (4.7)
1.8. Radiotherapists	2 (2.3)
1.9. Dermatologists	2 (2.3)
1.10. Pneumologists	1 (1.2)
2. Type of prescription*	
2.1. Paper order form	69 (80.2)
2.2. Electronic chemotherapy ordering system	31 (36.0)
2.3. Printed medical order form	22 (25.6)
Dispensing	
3. Staff that dispense oral chemotherapy*	
3.1. Pharmacists	81 (94.2)
3.1.1. Role of ambulatory pharmacist (only)	39 (48.1)
3.1.2. Role of oncology pharmacist (only)	19 (23.5)
3.1.3. Both roles	23 (28.4)
3.2. Nurses	
3.2.1. Pharmacy nurses	15.(17.4)
3.2.2. Day hospital nurses	6 (7.0)
3.3. Pharmacy technicians	28 (32.6)
3.4. Others	16 (18.6)
4. Place of dispensation*	
4.1. Hospital pharmacy	77 (89.5)
4.2. Day hospital surgery	11 (12.8)
4.3. Ambulatory care pharmacy	9 (10.5)
4.4. Specific oncology pharmacy surgery	2 (2.3)
Patient education	
5. Oral chemotherapy that generate visits	
5.1. Any oral agent	63 (73.3)
5.2. Some of them	19 (22.1)
5.3. Not applicable	4 (4.6)
6. Place of patient education*	*82 sites*
6.1. Hospital pharmacy	72 (83.7)
6.2. Hospital surgery	13 (15.1)
6.3. Ambulatory care pharmacy	8 (9.3)
6.4. Specific oncology pharmacy surgery	2 (2.3)
7. Type of visits (initial, successive, clinical trials)*	
7.1. Initial patient education	82 (95.3)
7.2. Successive visits	54 (62.8)
7.3. Clinical trials	4 (4.7)

Table 2 continued

	N (%) of sites
8. Staff involved in patient education*	*82 sites*
8.1. Pharmacists	81 (98.8)
8.1.1. Role of ambulatory pharmacist (only)	37 (45.1)
8.1.2. Role of oncology pharmacist (only)	22 (26.8)
8.1.3. Both roles	22 (26.8)
8.2. Nurses	
8.2.1. Pharmacy nurses	11 (13.6)
8.2.2. Day hospital nurses	8 (9.9)
8.3. Pharmacy technicians	12 (14.8)
8.4. Others	4 (3.7)
9. Patient specific resources employed*	84 (97.7)
9.1. GEDEFO triptychs	62 (73.8)
9.2 Own designed papers	45 (53.6)
9.3. Drug information by industry	15 (17.9)
9.4. Personalized treatment calendars	12 (14.3)
9.5. Other resources	4 (4.7)
10. Control adherence (how evaluated)*	46 (53.4)
10.1. Pill counts	24 (52.2)
10.2. Rates of prescription refills	16 (34.8)
10.3. Specific questionnaires	8 (17.4)
10.4. Dispensing exact number of doses	1 (2.1)
10.5. Electronic medication monitor	1 (2.1)
10.6. Monitor blood drug levels w. HPLC	1 (2.1)
11. Additional safety practices*	50 (58.1)
11.1. Double checks calculate dose	36 (41.9)
11.2. Barcode scan	11 (12.8)
11.3. Specific questionnaires	6 (7.0)
11.4. Others	13 (15.1)

* More than one answer for each question may be possible

pharmacy surgery is a novel specific consultation performed by at least one oncology pharmacy specialist (Board Certified Oncology Pharmacist) that provides expert oncology pharmacy services. These services include recommendations design, implementation, monitoring and modify pharmacotherapeutic plans to optimize outcomes in patients with malignant diseases. More than half hospitals also performed successive visits (62.8 %) and some settings performed clinical trials education visits (4.7 %). As expected, a pharmacist was almost always involved in these visits (98.8 %). This pharmacist had the role of oncology pharmacist (44, 54.3 %) or the role of ambulatory care pharmacist (59, 72.8 %). Other staffs involved in the visit were nurses, pharmacy technicians and others.

Most of the times (97.7 % of cases, patient specific drug information (PSDI) was provided to facilitate understanding the treatment even without a formal visit (Table 2). In addition, almost half of positive respondents stated that they employed more than one written resource (47.6 %). Precisely these hospitals (84 cases) provided PSDI of the GEDEFO society (GEDEFO triptychs,) (73.8 %); own hospital designed PSDI (53.6 %); written drug information provided by the industry (17.9 %); personalized treatment calendars (e.g. Infowin®) (14.3 %), and other resources (4.7 %) (EMA information to patients and carers, administration information sheet of specific oncology pharmacy software, Micromedex® care notes™). Almost half of positive respondents (47.6 %) stated that they employed more than one written resource.

Monitoring (control adherence)

Adherences measures were implemented in 46 (53.4 %) of the respondent hospitals. There was a wide range of approaches (Table 2), the most important included pill counting (52.2 %) and extrapolation with the rates of prescription refill (34.8 %). Other ways to measure adherence are shown in Table 2. On average, a quarter of these hospitals ($n = 11, 23.9$ %) performed more than one strategy to assess adherence to oral chemotherapy treatment.

Finally, other additional safety practices to improve management of these drugs were carried out in 50 hospitals (58.1 %). These safety practices were double checks of the calculated dose (41.9 %), barcode scan (12.8 %), specific questionnaires (7.0 %) and others (15.1 %), such as batch/expire date traceability, double check of dispensed medication or specific interviews, among others.

General assessment

There were 32 hospitals (37.2 %) with level I of safety and adherence practices, 38 hospitals (44.2 %) accomplished level II, 16 (18.6 %) hospitals attained level III (Fig. 1).

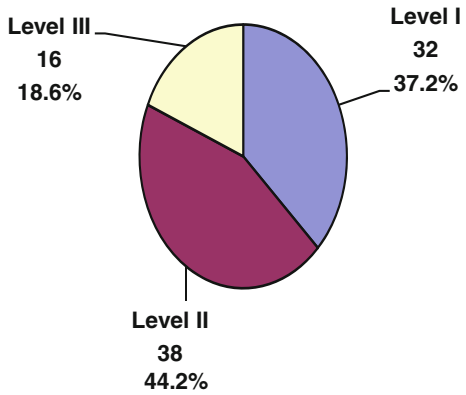

Fig. 1 Classification of respondent hospitals according to their implemented safety practices

It was performed a univariate analysis for hospital parameters and number of chemotherapy formulations prepared by year. This analysis was carried out for each level of safety (levels I to III). The number of chemotherapy formulations prepared by year tended to be lower among the hospitals in level I (20 [46.5 %] *vs.* 12 [27.9 %], $P = 0.074$). Moreover, the hospitals included in level II prepared 15,000 or more intravenous chemotherapy dilutions per year (14 [32.6 %] *vs*. 24 [55.8 %], $P = 0.030$]. In the logistic regression analysis, no independent factors significantly associated with each level of safety were found (data not shown).

Discussion

In this survey of 86 Spanish hospitals (50.9 % of targeted hospitals), the majority of responding hospitals were public, general, and teaching hospitals with more than 200 beds. A variable implementation of safety and adherence practices of oral chemotherapy management was observed. Main discrepancies were found in electronic prescription of oral chemotherapeutic drugs and in monitoring adherence. The results also indicated that a minimum level of safety has been established in most centres. There were 32 hospitals (37.2 %) with level I of safety and adherence practices, 38 hospitals (44.2 %) accomplished level II, 16 (18.6 %) hospitals reached level III. No hospital-related variables correlated with any level of safety, so that there is a need to ensure the widespread of safety practices on oral chemotherapy.

In the prescribing step of oral chemotherapeutic agents, the large majority of prescriptions were obviously medical oncologists and haematologists. In Spain, these specialties cover specifically the pharmacological treatment of cancer using drugs administered by all routes. However, it is observed that physicians of other medical specialties are currently prescribing oral chemotherapy and this practice is estimated that represents, depending on a particular oral anticancer drug, from 5 % to more than 20 % of cases. [19] It was stated that the belief of lower toxicity of oral anticancer drugs or the easiness of administration outside the hospital enhanced the outpatient prescription of these agents by clinicians of other specialties. [19].

There is a higher degree of awareness regarding safety risks associated with oral chemotherapy as shown by the growing number of hospitals that used an electronic chemotherapy ordering system to prescribe oral chemotherapeutic drugs. In an US survey, electronic prescribing was done in 16 % of centres and 12 % of centres used preprinted prescriptions form [17]. Computerized prescription order entry system proved to be an effective system to reduce prescribing errors of oral chemotherapy [20]. However, the paper order form was still the most frequently type of prescription. This is consistent with the US survey where most of respondents reported that oral prescriptions were handwritten (71 %) [17].

In this study, the pharmacist was the main health care staff involved in the dispensing process and the hospital pharmacy was the most frequently the place for collecting medication. Patient education by pharmacists is recognized as a crucial component of optimal patient care [21], which is also statistically significantly associated with improved patient outcomes and compliance [15]. Currently, the specialty of Oncology Pharmacy was a reality in Spanish hospitals integrated in a multidisciplinary team having a strategic situation between treatment and patients [22]. These specialty pharmacies may provide and additional level of safety checks and oncology knowledge applied to this process. Some authors suggested that, whenever possible, a pharmacist with experienced in oncology should be directly involved in dispensing oral chemotherapy to minimize potential errors [10]. Moreover, almost all the pharmacist performed an initial patient education intervention and more than a half performed successive visits. This patient education is crucial to avoid or minimize potential problems with oral chemotherapy (complex dosing regimens, interactions with other medication/meals, dysphagia/nausea/vomiting, unique toxicity profile of each agent, adherence, etc.) and maintain the advantages and efficacy of oral agents [23]. In a focus group study, patients on oral chemotherapy treatment described a need for more comprehensive patient education at the initial prescribing encounter, particularly regarding side effects and suggested frequent, provider-initiated follow-up [24]. They also demanded the equivalent resources and support systems provided in clinical trials. In the US survey, 95 % of respondents indicated that pharmacists were also responsible with physicians for educating patients about use these medications [17].

In these visits, some type of patient specific drug information was used in 97.7 % of cases and nearly half of respondents stated that they employed two or more different resources (47.6 %). To enhance patient understanding and adherence, pharmacies provide printed materials (own hospital or GEDEFO triptychs), individualized calendars (designed by specific pharmacological programs) and, in some cases, pre-loaded pillboxes to assist patients in their medication count. The US survey did not specifically address this issue, however, the authors stated that pharmacy services may be underused despite the widely availability of on-site pharmacies and consultation with a pharmacist [17]. Other authors stated that pharmacy services should be encouraged because it may facilitate adherence [25].

A great variety of different approaches to control of adherence was performed at the time of the survey in more than a half of the hospitals (53.4 %). In fact, several studies

have examined the degree of adherence (ranging from 20 to 100 %) to oral agents but all are fraught by the lack of a standardized tool with which to measure it [26, 27]. Unfortunately, there are currently no well-established mechanisms to assess adherence prospectively [2]. This fact may explain that some Spanish pharmacists performed more than one method to assess adherence. Moreover, the lack of response to an oral chemotherapy may be explained by a true chemotherapy resistance or non-adherence. So, adherence is a major issue to be discussed at the beginning and during all the therapy. Suboptimal adherence and discontinuation of therapy both may adversely impact the efficacy and toxicity of a medication, it is important that they be measured and maximized [25]. It was reported that early discontinuations and non-adherence to hormonal therapy were common and associated with increased mortality [9]. In the US survey, nearly a quarter of respondents recognized no formal process for monitoring adherence Weingart et al. [17] found that 10 comprehensive cancer centres reported asking patients to bring in pill diaries and 9 reported using pill counting to routinely monitor adherence [17].

The heterogeneity of the different implemented safety practices on oral chemotherapy reflects a lack of general consensus to address this new scenario. International guidelines often include general recommendations for chemotherapy as a whole or focused on administration only [11, 12]. In fact, it is advised that prescribing, dispensing and administrating oral chemotherapy should be carried out and monitored to the same standard as parenteral chemotherapy [10]. Moreover, efforts have been done to provide some good clinical practice guidelines for the provision of pharmacy services to patients receiving oral chemotherapy [13, 16]. Additionally, resources and attention by the health authorities and oncology as well as pharmacy communities are needed to reach a higher degree of safety. However, pharmacy services in Spanish hospitals have rapidly adopted different measures to overcome emerging risks and vulnerabilities of safety measures because of the increasing use of oral chemotherapy.

The lack of differences in hospital-related variables within each level of safety may be due to the fact that many of the respondent hospitals had similar characteristics. It is also well known that most hospitals in our country are public, general, and university-affiliated hospitals, which agrees with the present findings. Incidentally, there is a tendency regarding the number of chemotherapy preparations in level I. In level I, the chemotherapy preparations tended to be lower, and this characteristic may be in relation with a lower level of safety practices on oral chemotherapy. Oral chemotherapy and many targeted therapy agents may carry the same risks in terms of potential error and toxicities as intravenously given chemotherapy and must be in accordance to the same standards applied to parenteral chemotherapy [13]. The increasing number of chemotherapy preparations may guide the adoption of computerization of chemotherapy prescription and this proves to lead to fewer errors as well as safety improvement [28].

This study has several limitations, mainly the lack of data for non-responders. Safety practices at these sites may be different that those recorded in responders to the survey. It is unknown if this can affect our final conclusion. Also the safety measures may differ across clinicians and treatment regimens. On the other hand, the present findings may be different than actual circumstances due to the increasing number of oral chemotherapeutic agents recently approved. As for many other surveys, there was no external monitoring of the responses and the definitions used may vary from those used in other countries.

Further research to assess periodically the implementation of safety practices in oral chemotherapy is needed as well as to develop better international consensus guidelines for safety practices in cancer patients treated with oral chemotherapeutic agents.

Conclusion

In conclusion, results of the present survey show that the majority of hospitals in Spain have established different safety practices for oral chemotherapy, with pharmacists playing a major and crucial role. However, the characteristics of these practices vary in the different hospitals, and more efforts are needed to ensure the widespread adoption of more uniform safety measures. There are significant opportunities for improvement, particularly with regard to electronic prescription of oral chemotherapy and monitoring adherence.

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References

1. O'Neill VJ, Twelves CJ. Oral cancer treatment: developments in chemotherapy and beyond. Br J Cancer. 2002;87:933–7.
2. Weingart SN, Brown E, Bach PB, Eng K, Johnson SA, Kuzel TM, et al. NCCN Task Force Report: oral chemotherapy. J Natl Compr Canc Netw. 2008;6(Suppl 3):S1–14.
3. Petrelli NJ, Winer EP, Brahmer J, Dubey S, Smith S, Thomas C, et al. Clinical Cancer Advances 2009: major research advances in cancer treatment, prevention, and screening–a report from the American Society of Clinical Oncology. J Clin Oncol. 2009;27:6052–69.
4. Liu G, Franssen E, Fitch MI, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. J Clin Oncol. 1997;15:110–5.
5. Catania C, Didier F, Leon ME, Sbanotto A, Mariani L, Nole F, et al. Perception that oral anticancer treatments are less efficacious: development of a questionnaire to assess the possible prejudices of patients with cancer. Breast Cancer Res Treat. 2005;92:265–72.
6. Jensen LH, Osterlind K, Rytter C. Randomized cross-over study of patient preference for oral or intravenous vinorelbine in combination with carboplatin in the treatment of advanced NSCLC. Lung Cancer. 2008;62:85–91.
7. Weingart SN, Toro J, Spencer J, Duncombe D, Gross A, Bartel S, et al. Medication errors involving oral chemotherapy. Cancer. 2010;116:2455–64.
8. Font R, Espinas JA, Gil-Gil M, Barnadas A, Ojeda B, Tusquets I, et al. Prescription refill, patient self-report and physician report in assessing adherence to oral endocrine therapy in early breast cancer patients: a retrospective cohort study in Catalonia. Spain. Br J Cancer. 2012;107:1249–56.
9. Hershman DL, Shao T, Kushi LH, Buono D, Tsai WY, Fehrenbacher L, et al. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. Breast Cancer Res Treat. 2011;126:529–37.
10. Dooley M, Carrington C. Recommendations for managing patients receiving oral chemotherapy and target therapies. Asia Pac J Clin Oncol. 2008;4:122.
11. ISOPP standards of practice. Safe handling of cytotoxics. J Oncol Pharm Pract. 2007;13(Suppl):1–81.
12. Jacobson JO, Polovich M, Gilmore TR, Schulmeister L, Esper P, Lefebvre KB, et al. Revisions to the 2009 american society of clinical oncology/oncology nursing society chemotherapy administration safety standards: expanding the scope to include inpatient settings. J Oncol Pract. 2012;8:2–6.
13. Carrington C, Stone L, Koczwara B, Searle C, Siderov J, Stevenson B, et al. The Clinical Oncological Society of Australia (COSA) guidelines for the safe prescribing, dispensing and administration of cancer chemotherapy. Asia Pac J Clin Oncol. 2010;6:220–37.
14. Gandhi TK, Bartel SB, Shulman LN, Verrier D, Burdick E, Cleary A, et al. Medication safety in the ambulatory chemotherapy setting. Cancer. 2005;104:2477–83.
15. Beney J, Bero LA, Bond C. Expanding the roles of outpatient pharmacists: effects on health services utilisation, costs, and patient outcomes. Cochrane Database Syst Rev. 2000:CD000336.
16. SHPA Standards of Practice for the Provision of Oral Chemotherapy for the Treatment of Cancer. J Pharm Pract Res. 2007; 37:149–52.
17. Weingart SN, Flug J, Brouillard D, Morway L, Partridge A, Bartel S, et al. Oral chemotherapy safety practices at US cancer centres: questionnaire survey. BMJ. 2007;334:407.
18. Bonal J, Castro I, Duran J. Trends in clinical pharmacy in Spain. Ann Pharmacother. 1980;14:259–65.
19. Colomer R, Alba E, Gonzalez-Martin A, Paz-Ares L, Martin M, Llombart A, et al. Treatment of cancer with oral drugs: a position statement by the Spanish Society of Medical Oncology (SEOM). Ann Oncol. 2010;21:195–8.
20. Collins CM, Elsaid KA. Using an enhanced oral chemotherapy computerized provider order entry system to reduce prescribing errors and improve safety. Int J Qual Health Care. 2011;23:36–43.
21. Keely JL. American College of Physicians-American Society of Internal M. Pharmacist scope of practice. Ann Intern Med. 2002;136:79–85.
22. Alminana M. Mangues Bafalluy MA, Santos Ramos B [Spanish presence in BPS accreditation]. Farm Hosp. 2010;34:314–6.
23. Aisner J. Overview of the changing paradigm in cancer treatment: oral chemotherapy. Am J Health-Syst Pharm. 2007;64:S4–7.
24. Simchowitz B, Shiman L, Spencer J, Brouillard D, Gross A, Connor M, et al. Perceptions and experiences of patients receiving oral chemotherapy. Clin J Oncol Nurs. 2010;14:447–53.

25. Ruddy K, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. CA Cancer J Clin. 2009;59:56–66.
26. Partridge AH, Avorn J, Wang PS, Winer EP. Adherence to therapy with oral antineoplastic agents. J Natl Cancer Inst. 2002; 94:652–61.
27. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353:487–97.
28. Voeffray M, Pannatier A, Stupp R, Fucina N, Leyvraz S, Wasserfallen JB. Effect of computerisation on the quality and safety of chemotherapy prescription. Qual Saf Health Care. 2006; 15:418–21.