

Original Article | The impact of ROTS (Raadpleging voor patiënten op Orale antitumorale Therapie Sint-Lucas Gent) on oral anticancer drug use: a 5-year status update

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KEYWORDS

Oral anticancer therapy, oncology pharmacist, oncology pharmacy service, tyrosine kinase inhibitors (TKI), multidisciplinary outpatient oncology clinic, cancer supportive care

ABSTRACT

BACKGROUND AND AIM

Clinical pharmacists (CPs) can give in-depth education to patients regarding their treatment with oral anticancer therapy (OACT) in order to ensure the medication is taken correctly and the adverse events (AEs) are managed effectively. The purpose of this study was to evaluate the role and usefulness of an outpatient oncology clinic, ROTs (Raadpleging Orale antitumorale Therapie Sint-Lucas Gent) over a nearly 5 year real life practice period.

METHODS

A retrospective analysis of the CPs interventions was performed. Additionally, both onco-physicians and patients on OACT, whether or not included in the ROTs, were invited to participate in a survey regarding the general satisfaction of the ROTs project.

RESULTS

From April 2010 until January 2015 2974 interventions for 181 patients were registered. The most frequent interventions were AE monitoring and management (43.21%), pill count (26.26%) and medication reconciliation and review (22.06%). The patient survey (n=40) showed that ROTs patients were better informed about all aspects of the therapy (70% vs. 35%) and the 10 onco-physicians surveyed were highly satisfied about the collaboration and would recommend ROTs with a score of 4.9±0.27/5.

DISCUSSION AND CONCLUSION

This study is a good example of delivering clinical care by CPs in an outpatient clinic and to help patients overcome barriers to achieve a more optimal therapy while maintaining their quality of life. However significance could not be determined due to the lack of a comparable group. This study can set a base for further improvement of an outpatient oncology clinic in all hospitals. This outpatient clinic led to a lower threshold for patients to contact a CP resulting in an earlier diagnosis of the AEs and drug drug interactions and potentially to earlier interventions and alterations of the treatment plan.

INTRODUCTION

In the last decade, different studies have shown an increase in

the use and variety of oral anticancer drugs (OACD).⁽¹⁻⁴⁾ As cancer is becoming more and more a chronic illness, new therapies and new combinations of therapies are explored. In this regard, targeted treatment involving OACD is often used as monotherapy or in combination with other traditional intravenous anticancer therapies to treat cancers such as, among others, breast cancer, liver cancer, lung cancer, as well as hematological malignancies like multiple myeloma or myeloid leukemia. This has caused a major shift from monitored inpatient, intravenous therapy, to self-administered oral therapy. The latter therapy is administered away from the conventional hospital setting or infusion clinic, whereby the patient is responsible for monitoring, identifying and managing adverse drug events (ADEs) between clinic visits, which can sometimes have an interval of several months. Consequently, the risk of dosing errors, medication and/or food interactions and compromised therapeutic efficacy due to poor medication adherence is increased.^(5,6)

Poor medication adherence can occur due to misunderstanding or confusion about the treatment regimen, failure to remember dosing regimens or failure in management of ADEs. Home treatment can also lead to unintended exposure of family members to hazardous substances. These issues are less prevalent with parenteral therapy which is administered under direct supervision of HPs to ensure treatment completion, to monitor ADEs, and to guarantee appropriate disposal of waste. Overall, these issues that arise with OACD-therapy demonstrate the need for improved patient monitoring and self-management.⁽⁴⁾ In this setting, clinical pharmacists (CPs) can play a unique role in the multidisciplinary oncology healthcare team. As part of the team, CPs conduct the following: medication review, patient education to improve patients' understanding of medication regimens, supporting adherence and monitoring of ADEs and self-management skills. In this regard, the ROTs (Raadpleging voor patiënten op Orale antitumorale Therapie Sint-Lucas Gent) outpatient clinic was initiated in AZ Sint-Lucas Gent, a general hospital (901 beds) in Belgium, in 2010 as a multidisciplinary outpatient service to improve pharmaceutical care to patients on OACD treatment. It focuses on providing specialized counseling, support and follow-up (by clinic visit, phone or mail) in order to provide a (cost-) effective therapy and to improve patients' adherence in close collaboration with all involved healthcare providers (HPs).

Pharmacist-led oral chemotherapy management programs are currently being developed to address these unique challenges.⁽⁵⁾ Unfortunately, only a few reports have been published to date. The purpose of this current research project was to evaluate the role and usefulness of this outpatient clinic. In a retrospective part, the treatment duration, ADEs, relevant drug drug interactions (DDIs) as well as contact with other HPs were analysed over a nearly 5 year real-life practice period. In a prospective part, the general satisfaction about the information provided by the CPs was evaluated. Therefore, a survey was developed for patients from the outpatient clinic and a control group of patients receiving their OACD directly from the hospital pharmacy. In addition, onco-physicians were interviewed regarding the collaboration within the outpatient clinic.

Overall, based on the obtained results and acquired knowledge from the literature, this research project aimed to examine which important role CPs can play and to gain future perspectives about the role of the CPs in the education and support of patients on OACD in an outpatient clinic.

METHODS

SETTING, PATIENT INCLUSION, DATA COLLECTION AND ANALYSIS

The study consists of 2 parts. The first part is a retrospective analysis of the CP interventions.

In the retrospective study all patients, aged 18 years or older, starting treatment with tyrosine kinase inhibitors (TKIs) dispensed in the ROTS outpatient clinic from AZ Sint-Lucas Gent, a general hospital (901 beds) in Belgium, between 1 April 2010 and 1 January 2015 were included. All CP interventions for these patients were recorded in the patient medical file. The analysis consisted of collecting patient demographics (gender, age, tumor type, TKI, co-medication) and analysis of the registered interventions during the first and follow up visits like the number of actions concerning monitoring and management of ADEs and the type of ADEs, the medication reconciliation and review, the reason to contact other HPs, pill counts and other interventions. The duration of the clinic visits and the respective interventions was determined. The collected data were analyzed in Microsoft Office Excel®. Descriptive statistics were used to describe the participants' age and gender.

In the prospective study, a self-reported questionnaire was implemented with closed questions about the general satisfaction of the provided information and therapy adherence for all patients included in the study between 25 September 2017 and 1 March 2018. Two groups of patients were surveyed, the ROTS group included patients with a TKI treatment counseled at the outpatient clinic and the control group included patients treated with Zytiga® (abiraterone) or Xtandi® (enzalutamide) dispensed by the hospital pharmacy without counseling by a CP. Satisfaction and adherence was assessed by a five-point Likert rating scale. In addition, a survey was obtained from all onco-physicians in the ROTS project involving closed questions regarding satisfaction and collaboration with the CP. Answers were assessed by the same five-point Likert rating scale. The physicians were informed by mail and the questionnaire was received anonymously via paper.

The data retrieved from the completed questionnaires were analyzed using Microsoft Office Excel®. Descriptive statistics were used to analyze the patients' response in order to describe the participants' median age, gender and education. If applicable, the mean and standard deviation was computed for each survey item separately.

ETHICAL CONSIDERATION

Due to the retrospective design of the first part of the study as well as the lack of patient contact and intervention, a patient consent was not required nor obtained. For the second part of the study, patients' and physicians' consents to participate in the survey were obtained after they received a detailed written explanation of the study. Personal information was protected in the aggregated data. Approval for data analysis was obtained of the Ethics Committee of AZ Sint-Lucas Gent (project number EC 2017/30) and Ghent University Hospital (project number EC 2017/1021).

RESULTS

RETROSPECTIVE ANALYSIS OF THE INTERVENTIONS IN THE ROTS OUTPATIENT CLINIC

In total, 181 first clinic visits for 181 patients (mean age of 66 years, 41% male) and 1455 follow-up visits were performed.

Table 1 illustrates the demographics and clinical characteristics of the patients. The first clinic visit lasted about 32 minutes whereas the follow-up visits lasted approximately 19 minutes. During the clinic visits, different interventions were performed by the CP. Of all consultations, 25% (405) was done via telephone (98.77%) or e-mail (1.23%). Figure 1 illustrates the number of patient contacts per TKI outside the outpatient clinic. Further, the main reasons for contact via e-mail or phone involved management of ADEs (69.88%), interaction check (12.35%), advice about intake or other medication related questions (5.44%) and any other reason (12.34%). Figure 2 illustrates the reasons for contact via telephone or e-mail.

OACD	Total number of patients	Gender m/f	Age (years), Mean \pm SD (Range)	Type of tumor (%)
Erlotinib	47	31/16 (66%/34%)	66 \pm 9.09 (40-79)	NSCLC Squamous cell carcinoma (11%) /adenocarcinoma (89%)
Lapatinib	20	0/20 (0%/100%)	61 \pm 10.87 (40-79)	HER2/neu+ breast cancer + capecitabine (95%) / +aromatase inhibitor (5%)
Gefitinib	15	4/11 (27%/73%)	67 \pm 12.68 (52-92)	NSCLC-adenocarcinoma (100%)
Sunitinib	25	18/2 (90%/10%)	67 \pm 7.48 (52-81)	VHL-haemangioblastoma (4%) /mRCC (96%)
pazopanib	17	8/9 (47%/53%)	69 \pm 11.75 (42-82)	mRCC (94%) / Soft-tissue sarcoma (STS) (6%)
Sorafenib	9	6/3 (67%/33%)	67 \pm 6.94 (61-78)	mRCC (56%) / HCC (33%) / Thyroid carcinoma (11%)
Axitinib	6	8/12 (40%/60%)	62 \pm 5.24 (54-67)	mRCC (100%)
Vemurafenib	5	2/3 (40%/60%)	66 \pm 16.73 (44-85)	BRAF-mutation+ melanoma
Everolimus	37	8/29 (24%/76%)	66 \pm 9.59 (41-88)	HER2/neu+ - advanced breast cancer (46%) mRCC (54%)

Table 1: The demographic and clinical characteristics of the patients for the different OACD

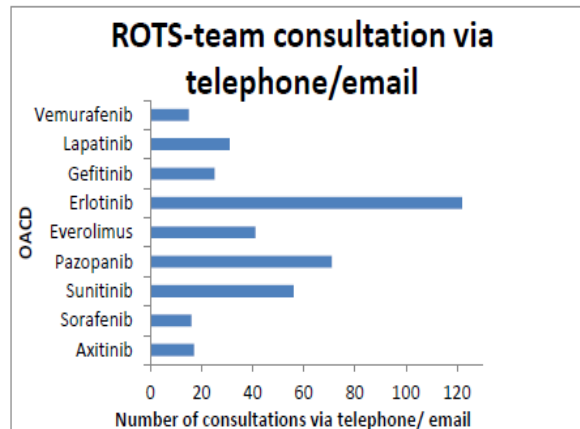


Figure 1: The number of patient contacts per TKI outside the outpatient clinic via telephone or email (total number = 405)

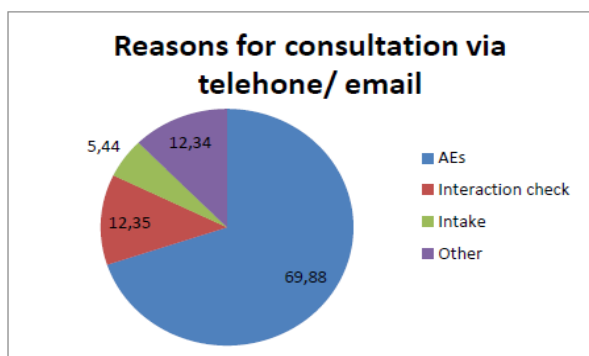


Figure 2: The reasons for consultation of the CP (%) via telephone or email

Overall, 2974 interventions were performed during the study period. The most common interventions for all TKIs involved firstly 'AE monitoring and management' (43.21%) on a monthly basis. Fifty eight patients (32%) temporarily interrupted their treatment to manage AEs and had a dose adjustment before or after therapy interruption. 'Medication reconciliation and review' involved 22.06% of the interventions and for 166 (92%) patients with co-medication a medication schedule was generated. A total of 105 drug-drug interactions (DDIs) was detected for 78 (43%) patients. For 8 (10%) of these patients no action was required, but treatment was interrupted for 8 (10%) others. For the remaining 80% a recommendation or an alternative was suggested by the CP and 92% of these advices was accepted by the treating oncophysician. A 'pill count' performed during every visit represented 26.26% of the interventions. However, the exact amount of residual pills was not always registered but often only expressed as "enough pills" or "adherent", therefore the adherence could not be calculated correctly. Lastly, 'contact with other HPs' (5.68%) and 'Other' interventions (2.79%) like advice about correct intake upon dose adjustment, treatment schedule information for patients experiencing swallowing difficulties,... were also performed. Figure 3 shows which HPs were contacted (5.68% of the interventions) and illustrates that the general practitioners (GPs) were contacted most often, followed by dieticians and dermatologists. Adverse drug events were the main reason to contact other HPs. A total of 83 other interventions involved advice regarding intake after vomiting, composition of a preparation and referral to a psychologist for depression.

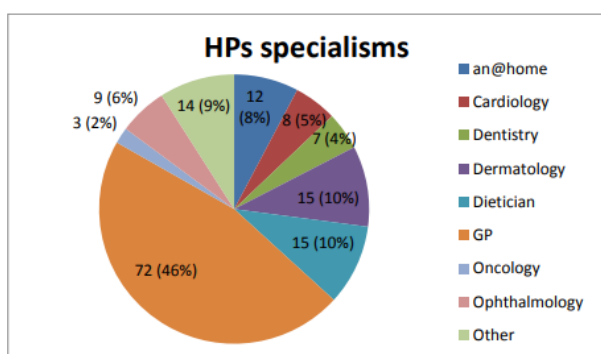


Figure 3: The different HPs who were contacted, "an@home"= Afinitor Novartis oncology service at home, Other: orthopedic surgery, podology, psychology, nefrology and nursery.

PROSPECTIVE SURVEY TO DETERMINE SATISFACTION AND/OR ADHERENCE SURVEY FOR PATIENTS

In the prospective study 20 ROTS patients (25% male) and 20 control patients (100% male) were included with a median age

above 70 years. Table 2 illustrates the relevant results of the questionnaire for both control and ROTS group. The satisfaction score of the patients regarding the provided information varied between 3 and 5 out of 5 with a mean of 4.4 ± 0.6 vs. 4.7 ± 0.48 (control vs. ROTS group). Patients who preferred extra verbal or written information scored the provided information the lowest or did not fill in a score at all. In addition patients were asked to score the adherence to the medication schedule revealing a score between 3 and 5 (5 = not difficult), with a mean of 4.2 ± 0.81 vs. 4.5 ± 0.61 . The ROTS patients needed to answer 2 extra questions about the outpatient clinic. Fourteen (70%) ROTS patients indicated that they had contacted the clinical pharmacist at least once outside the opening hours of the outpatient clinic, of which 12 (60%) via phone, 1 (5%) via email and 1 (5%) via both phone and email. The mean score that was given for 'accessibility of the outpatient clinic' and 'satisfaction about the provided solution' was 4.6 ± 0.63 on a scale of 5, indicating that the patients were very satisfied. In contrast, in respect to the obtained results, no significant difference in adherence between men and women, between the different drugs as well as between the different age groups could be determined. Therefore, the results will only be used in order to optimize the manner of providing information.

Questions	Control group	ROTS group
Enough time to ask questions to oncologist (%)	18 (90%)	20 (100%)
Prefer written instruction (leaflet or information brochure)	2 (10%)	0 (0%)
Prefer verbal instruction	1 (5%)	0 (0%)
Providing information on the hospital website	7 (35%)	6 (30%)
Did you inform your GP about your OACD?	13 (65%)	16 (80%)
Did you inform your GP + community pharmacist about your OACD?	9 (45%)	10 (50%)
Adherence (correct medication intake)	20 (100%)	20 (100%)
Did you once forgot to take your OACD?	2 (10%)	0 (0%)
Did you change your schedule at least once?	1 (5%)	3 (15%)

Table 2: Relevant results of the questionnaire for both control and ROTS group

SURVEY FOR THE ONCO-PHYSICIANS

Table 3 illustrates the results of the survey for oncologists involved in the outpatient clinic. A total of 10 onco-physicians participated. They were satisfied with the collaboration with the CPs and would recommend it to other physicians and hospitals. This was reflected by a high mean recommendation score of 4.9 ± 0.27 out of 5. Further, the physicians were asked to give their idea about the effect on treatment duration and cost-effectiveness. This was, however not answered by all physicians probably due to the subjective nature of this question, 4.3 ± 0.67 and 3.6 ± 0.79 respectively. Finally, some physicians added comments regarding the outpatient clinic like good collaboration, excellent!, making use of apps for example for reporting ADEs,...

Questions	Mean score (/5)	N
Contacting the ROTS when a new patient starts with treatment	4.6	10
Accessability of the ROTS	4.6	10
Satisfaction about the collaboration	5	10
Impression patients are better informed and educated	4.8	10
Impression prolonged duration of treatment	3.6	7
Cost-effectiveness	4.3	8
General satisfaction of the patient	4.6	10
Providing information on the website	4.9	10

Table 3: Results of the questionnaire for oncologists

DISCUSSION

CPs can give in-depth education to patients regarding their treatment in order to ensure the medication is taken correctly and the ADEs are managed effectively. Therefore, it is

undeniable that CPs can play an essential role in patient compliance. In this regard, we have retrospectively analyzed the real life use of TKIs in a general hospital in Belgium. Such analyses were only possible because the hospital implemented a systematic dispensing of these drugs via an outpatient clinic called ROTS. Via the collected data we were able to have a complete overview by different specialism of all patients treated with OACD over a prolonged period of time. This research project analyzed 2974 interventions provided by the CPs during the almost 5 year real-life practice. According to literature three interventions proof to be essential to improve patients' adherence: ADEs monitoring and management, pill count and medication reconciliation and review. According to Deutsch et al., ADEs with OACD are the most common (39%) reason for discontinuation in the first two months of therapy and the second most common reason (28%) for missed and held doses. Moreover, 76% of the reported AEs occurred within the first month.⁽⁷⁾ If AEs are therefore left unreported, necessary dose adjustments may not be made as well as serious consequences may occur impacting both the quality of life (QoL) of the patient and further therapy. Hence, it was decided to implement this intervention because if the AEs are managed well this will also improve the medication adherence. There was a monthly follow up by the CPs and this resulted in early detection of ADEs. The type of ADEs were registered and grossly resembled the ADEs also seen in clinical trials. Often these ADEs were seen first by the CPs as the frequency of the patient contact was higher, particularly when the attending physician was a non-oncology clinical specialist. Most of the AEs were grade 1, which were often managed well by the CPs. Grades 2 and 3 AEs were communicated clearly to the involved physician, indicating a need for increased or/and extensive interventions, dose adjustments or interruption of treatment.

A pill count ensures that patients bring their residual medication to the clinic appointment to reduce wastage and to estimate adherence. Among patients with serious conditions, a mean possession rate (MPR) of 95% is often considered mandatory as a consequence of reduced efficacy and potential toxicity could be serious.⁽⁸⁾ Although, pills were counted during every clinical visit, the MPR could not be calculated in this study because the exact amount of residual pills was not always registered. In addition, the number of pills were often recorded as "enough pills" or "adherent", making it difficult to estimate the real adherence. However, the results of a simultaneous 1 year study (IPSOC) showed excellent adherence in some metastatic renal cancer patients. ⁽⁹⁾ To investigate the adherence, a prospective questionnaire was issued for both the ROTS patients and the prostate cancer patients where both groups showed excellent adherence. It should be noted that subjective findings must also be interpreted with caution as this was related more to the personal experience. Research on the cost-effectiveness of these interventions was relatively sparse and future aims would be to investigate this with a reliable tool to enable more accurate assessment of the adherence.

According to Darkow et al., TKI adherence decreased upon increase of the number of medications taken by the patient due to pill burden.^(10,11) Therefore, medication reconciliation was performed to obtain a complete medication list, in order to check the medication for appropriateness and DDI. In addition, a patient tailored intake-schedule was made for each patient based on the patients' lifestyles with the aim to improve adherence. In this study 166 patient showed co-morbidities, especially due to elderly age, and consequently had other co-

medications provided by the community pharmacy. Overall, 655 medication reviews were performed and 105 DDIs (15.57%) were detected in 78 patients (77% pharmacokinetic, 20% pharmacodynamic and 3% others). This was not surprising, since TKIs are known to be potent CYP-inhibitors, as well as CYP-substrates.⁽¹¹⁾ The monitoring or modification of the treatment was recommended to the treating physician and education on DDIs to minimize any unfavorable consequences for the patients was provided. Further, during the clinic visit, the effectiveness and safety of each medication was evaluated and was adjusted or interrupted, if needed, after consultation with the treating physician. Medication review was not only useful for detecting interactions and medication inappropriateness, but also for preventing and monitoring of AEs, in collaboration with oncologists and other HPs (e.g. check for preventive treatments and conditions that increase the risk of cardiac AEs, such as other QTc-prolonging agents).⁽¹²⁾ Other medication related discrepancies couldn't be assessed because of lack of data.

Aside from these three main interventions mentioned above, 'Contact with other HPs' was, although less frequent, an intervention to consider. According to a study involving the pharmacist's role in breast cancer patients, patients with cancer often interact with many different HPs (including physicians, nurses and pharmacists) and often receive conflicting information about how medication should be used. This problem may become even more complicated if the patient is also taking co-medication or is being treated with complex chemotherapy regimens.⁽¹³⁾ This emphasizes the importance of good communication and collaboration between the different HPs. The main reason for 'Contact with other HPs' was to achieve good AE management and detecting interactions. The outpatient clinic has put a lot of effort in managing and monitoring AEs, not only by the CPs but also through a collaboration with different HPs. In the outpatient clinic, supportive therapy to treat AEs comprised the majority of cases. We believe that the AEs were managed well as the CP provided support at every examination and maintained communicating with other HPs. However, these results were not significant due to the lack of a comparable group.

A part of the 'other' interventions that were performed, included improvement of adherence. The CP was able to proactively identify the patient-specific barriers regarding adherence and subsequently removed those barriers to aid patients to be successful in the intake of their medicines.

All patients on TKIs counseled in the outpatient clinic were included in the prospective study as it was not ethically justified to exclude patients from counseling only to have a control group. The only OACDs dispensed by the hospital pharmacy outside the outpatient clinic were Zytiga® (Abiraterone) or Xtandi® (Enzalutamide), subsequently patients having a treatment with abiraterone or enzalutamide were not counseled and were eligible as control group. The survey results were only used to obtain deeper insight in providing information and were clinically not significant. The questionnaire showed that patients in the outpatient clinic (70%) were better informed about all aspects of the therapy, compared to the patients outside the outpatient clinic (35%). Although all patients received information about their OACD from the physician and were relatively satisfied with the obtained information (4.4/5 (control group) versus 4.7/5 (ROTS group)). This emphasizes the importance of a good collaboration between the physician and the CP. The CP can facilitate the provision of information given by the physician.

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The majority of the patients not attending the outpatient clinic did not recognize a role for the CP, probably because they were not familiar with it. Nevertheless, by offering this service more and more in daily practice, CPs can play an important role and maximize patient contact to achieve a higher level of patient satisfaction and awareness. The adherence, based on the patient survey, was in both groups excellent and there were no reasons for intake failures or intake schedule changes. However these findings must be interpreted with caution as these are related to the personal, and hence subjective, experience of the patient. No difference in adherence between men and women could be determined, nor between the different drugs, nor between the different age groups. Further analysis with a comparable hospital as well as a comparable control group to obtain significant results is highly recommended.

The additional question for the ROTS patients regarding contacting the CP showed the necessity of follow-up as 70% of the patients had contacted the CP for therapy-related questions. Moreover, the satisfaction about the provided solution was high (mean of 4.7/5). Patients found pharmacist-led interventions in the oncology setting useful. As reported by a survey of patients in an outpatient oncology setting, 86% felt it was "necessary" to discuss initial treatment with a pharmacist, and 76% requested a pharmacist to be present at the follow-up visits. Moreover, 83% of patients stated they were willing to pay for the pharmacy service.⁽⁵⁾ The patients were aware of the toxicity and necessity of the correct use of their medication to succeed in therapy and because of this there was need for extra information provision by the CP. The idea of providing information regarding OACD on the hospital website appeared to be useful for limited number of patients. This could be related to the fact that the group mainly consisted of elderly who were not familiar with technology.

The physicians of the outpatient clinic were generally very satisfied with the collaboration with the CPs and would recommend this practice to other physicians and hospitals.

ACKNOWLEDGEMENTS

I want to thank the hospital pharmacists (my colleagues) and oncologists of AZ Sint-Lucas Gent for the collaboration and my supervisor and colleague clinical pharmacist Hendrickx Tine, for sharing her pearls of wisdom and to provide insight and expertise that greatly assisted this research. I would also like to show my gratitude to the chief hospital pharmacist Baert Mariëlle and prof Dr. Annemie Somers for comments that greatly improved the manuscript.

I'm also immensely grateful to the reviewers of BJHP for their comments on an earlier version of the manuscript, although any errors are our own and should not tarnish the reputations of these esteemed persons.

'The author(s) declare(s) that there is no conflict of interest'.

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