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Optimising pharmacotherapy in older cancer patients with polypharmacy

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Abstract

Objective: Polypharmacy is frequent among older cancer patients and increases the risk of potential drug-related problems (DRPs). DRPs are associated with adverse drug events, drug-drug interactions and hospitalisations. Since no standardised polypharmacy assessment methods for oncology patients exist, we aimed to develop one that can be integrated into routine care.

Methods: Based on the Systematic Tool to Reduce Inappropriate Prescribing (STRIP), we developed OncoSTRIP, which includes a polypharmacy anamnesis, a concise geriatric assessment, a polypharmacy analysis taking life expectancy into account and an optimised treatment plan. Patients ≥65 years with ≥5 chronic drugs visiting our outpatient oncology clinic were eligible for the polypharmacy assessment.

Results: OncoSTRIP was integrated into routine care of our older cancer patients. In 47 of 60 patients (78%), potential DRPs (n = 101) were found. In total, 85 optimisations were recommended, with an acceptance rate of 41%. It was possible to reduce the number of potential DRPs by 41% and the number of patients with at least one potential DRP by 30%. Mean time spent per patient was 71 min.

Conclusions: Polypharmacy assessment of older cancer patients identifies many pharmacotherapeutic optimisations. With OncoSTRIP, polypharmacy assessments can be integrated into routine care.

KEYWORDS

cancer, deprescribing, drug-related problems, geriatrics, medication assessment, polypharmacy

1 | INTRODUCTION

At the time of diagnosis, 55% of cancer patients in Europe are ≥65 years old (Ferlay et al., 2013). Due to demographic shifts and new treatment options with improved survival rates, cancer will primarily be a disease of the older adult. As age increases, the prevalence of multimorbidity and polypharmacy rises as well. Polypharmacy is defined as the chronic use of five or more drugs and it is associated with the occurrence of potentially inappropriate medications (PIMs) (Nightingale, Hajjar, Swartz, Andrel-Sendecki, & Chapman, 2015). PIMs are drugs used in situations where there is no or limited benefit and/or risks are increased (Beers et al., 1991). Consequently, the presence of PIMs is associated with a higher risk of adverse drug events, drug-related hospitalisation and unnecessary healthcare expenses (Gallagher, O'Connor, & O'Mahony, 2011). In older adults with cancer, a positive association was found between

polypharmacy and occurrence of PIMs (Reis, Santos, Jesus Souza, & Reis, 2017). Both polypharmacy and the occurrence of PIMs are frequently seen in this population, with polypharmacy in up to 84% of patients (Nightingale et al., 2015) and the prevalence of PIMs is reported to be around 50% (Nightingale et al., 2015; Reis et al., 2017).

The risk of adverse effects may be even more relevant for cancer patients because of the exposure to highly active antitumor therapies and the risk of drug-drug interactions with cancer treatment. Polypharmacy in cancer patients is associated with more grade III-IV chemotherapy-related toxicity (Hamaker et al., 2014). In case of a reduced life expectancy, it is appropriate to consider new goals of treatment, including all co-morbidities. Medication intended for long-term prevention can often be safely discontinued, as was demonstrated for statins (Kutner et al., 2015).

The appropriateness for older cancer patients of generic medication screening tools that exist for older patients have been previously reviewed (Whitman, DeGregory, Morris, & Ramsdale, 2016), such as the Screening Tool of Older Peoples' Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) criteria (Gallagher, Ryan, Byrne, Kennedy, & O'Mahony, 2008), Beers criteria (American Geriatrics Society, 2015, Beers Criteria Update Expert Panel, 2015) and the Medication Appropriateness Index (MAI) (Hanlon et al., 1992). While older cancer patients can benefit from applying any of these tools, none of these include all relevant aspects for this specific population such as potentially unnecessary medication, the patient's condition and the treatment goals (Whitman et al., 2016). Medication screening tools specifically designed for cancer patients are sparse. One good example of a practical cancer orientated tool is the "OncoPal deprescribing guideline" (Lindsay et al., 2015) which can be applied in the terminal six months of a patients' life. However, incurable cancer patients on active treatment often have a life expectancy beyond six months, making the tool less applicable to these patients.

Another valuable cancer-specific tool is the individualised medication assessment and planning (iMAP) for older outpatient cancer patients (Nightingale et al., 2017). iMAP is a structured assessment including a patient-involved medication assessment and an analysis of medication based on the identification of potential drug-related problems (DRPs). By looking for these potential DRPs, and not only PIMs, iMAP provides a more complete medication assessment, since DRPs include problems such as overtreatment, undertreatment and potential adverse drug events (Nightingale et al., 2017; Strand, Morley, Cipolle, Ramsey, & Lamsam, 1990).

iMAP has many similarities with the Systematic Tool to Reduce Inappropriate Prescribing (STRIP) method. This method is embedded in the Dutch multidisciplinary polypharmacy guideline (Dutch General Practitioners, Dutch Geriatric Society, Dutch Order of Medical Specialists, 2012). STRIP consists of five steps: (a) questioning the patient about their medication use, (b) conducting a structured pharmaceutical analysis by a pharmacist (also based on identification of potential DRPs), (c) agreeing on an optimised treatment plan by physician and pharmacist, (d) making the new treatment plan definite through shared decision-making with the patient and (e) following up and monitoring (Dutch General Practitioners, 2012). While STRIP is already commonly used in Dutch primary care, the method can be specified for cancer patients, for example by adding a practical (de)prescribing guide suitable for cancer patients. Therefore, we developed the "OncoSTRIP," a polypharmacy assessment method specifically optimised for cancer patients with the aim to integrate it into routine care of the older cancer patient.

2 | METHODS

2.1 | Setting and study population

The study protocol was designed as an exploratory prospective study. While not yet systematically embedded in the routine care of cancer patients, a polypharmacy assessment using STRIP is considered to be part of regular care in the Netherlands. The institutional review board concluded that the Medical Research Involving Human Subjects Act (WMO) did not apply to the study protocol and that an official ethics approval was not required. Although written informed consent was therefore not necessary, patients were informed by their oncologist/haematologist using a protocol summary before any data was collected. The OncoSTRIP was offered to patients ≥65 years with ≥5 chronic medications on active treatment that visited the outpatient oncology/haematology clinic of our community-based hospital between February 2016 and April 2017. Patients were free to decline participation. Patients that agreed to participate were scheduled for the OncoSTRIP method in alignment of their regular visits to the outpatient clinic, infusion centre or outpatient hospital pharmacy.

2.2 | OncoSTRIP method

With OncoSTRIP, the patients followed a structured stepwise polypharmacy assessment, which consecutively consisted of four individual components described in detail in the following section.

2.2.1 | Polypharmacy anamnesis

The goal of the polypharmacy anamnesis step was to collect all relevant information on the patients' medication use. Prior to the anamnesis visit with the patient, the pharmacist collected relevant background data, such as medical history and medication use according to the hospital and/or community pharmacy records. For the polypharmacy anamnesis visit, a structured questionnaire was used (Figure S1), in which the oncology drugs, supportive drugs, prescription drugs and possible over-the-counter drugs were discussed with the patient by a pharmacist. The following aspects were included: Type of drug, dose, indication, date of start, initial prescriber, effect, adverse drug effects, practical problems (including compliance) and if relevant, extra information on medical history. To allow shared decision-making, patients were asked which drugs they were willing to discontinue and which they highly valued.

TABLE 1 Patient characteristics

Characteristic	No. (%)[a]
N	60
Age, years (mean, range)	74 (50–87)
Sex	
Female	16 (27)
Male	44 (73)
Cancer type	
Solid malignancies	
Colorectal	14 (23)
Prostate	8 (13)
Breast	5 (8.3)
Melanoma	4 (6.6)
Renal cell	2 (3.3)
Oesophageal	2 (3.3)
Brain	2 (3.3)
Pancreatic	1 (1.7)
Endometrium	1 (1.7)
Lung	1 (1.7)
Haematologic malignancies	
Myeloma	9 (15)
Lymphoma	6 (10)
Leukaemia	3 (5.0)
Myelodysplastic syndrome	2 (3.3)
Staging	
Solid malignancies staging	
I	0 (0.0)
II	0 (0.0)
III	6 (10)
IV	31 (52)
Not applicable	2 (3.3)
Haematologic malignancies staging	20 (33)
Unknown	1 (1.7)
Number of drugs (mean, range)	
Total	13 (6–23)
Oncology	2 (0–6)
Oncology supportive	2 (0–7)
Chronic	9 (4–20)

[a]Data are depicted in frequencies and percentages, unless otherwise specified.

2.2.2 | Concise geriatric assessment

In parallel to the polypharmacy anamnesis, a nurse specialist or oncology nurse performed a concise geriatric assessment with the patient. The concise geriatric assessment consisted of scoring systems Adult Comorbidity Evaluation-27 (ACE-27) (Piccirillo, Tierney, Costas, Grove, & Spitznagel, 2004), Eastern Cooperative Oncology Group performance status (ECOG-PS) (Oken et al., 1982) and Geriatric-8 (G8) (Bellera et al., 2012), to evaluate comorbidity, performance and frailty respectively. Comorbidity, performance status and frailty are essential determinants of the treatment options, prognosis and goals of care, and therefore these were factors to consider when making the treatment plan.

2.2.3 | Polypharmacy analysis

The pharmaceutical analysis was structured by the evaluation of eight potential DRPs: requirement of additional drug therapy, unnecessary drug therapy, ineffective treatment, (potential) adverse effects, clinically relevant contraindications or interactions, underdosing, overdosing and practical drug use problems/optimisations. PIMs were identified by our newly developed "OncoSTRIP list of drugs suitable for deprescribing in older cancer patients" (Table S1) and categorised within the potential DRPs. This deprescribing checklist was based on the STOPP criteria (Gallagher et al., 2008), Beers criteria (American Geriatrics Society, 2015 Beers Criteria Update Expert Panel, 2015), "OncPal deprescribing guideline" (Lindsay et al., 2015), "Checklist for symptom stability after withdrawing medicines" (Potter, Flicker, Page, & Etherton-Beer, 2016) and available literature. Besides these explicit criteria, potential DRPs were also identified through the expertise of the clinical pharmacist and treating physician. If necessary, initial prescribers were contacted for further information.

2.2.4 | Polypharmacy treatment plan

After the analysis, the pharmacist's recommendations were reported in the patient's electronical medical record to the treating oncologist/haematologist for reviewing. Upon agreeing with the recommendations, the treating physician discussed the intended medication adjustments with the patient.

2.3 | Outcomes

Outcomes were the prevalence of potential DRPs and the proportion of pharmacotherapeutic recommendations. Furthermore, the acceptance rate of the recommendations was evaluated by reviewing patient's electronical medical and/or pharmacy records directly after the patient's consultation with the treating physician, and after median follow-up period of four months. Time invested in the different steps of the polypharmacy assessment was recorded as well. Finally, with univariate analyses (Fisher's or Fisher-Freeman-Halton exact test, statistical significance at $p < .05$), the outcomes of the concise geriatric assessment were tested for the prediction of the occurrence of recommendations, to identify patients most likely to benefit from polypharmacy assessment. For the statistical analyses, IBM SPSS version 21 was used.

3 | RESULTS

3.1 | Patient characteristics

None of the patients declined to participate in this study. Characteristics of the 60 patients that underwent a polypharmacy assessment are

TABLE 2 Most commonly used chronic drugs according to their pharmacologic category, with exception of the oncology drugs

Pharmacologic Category	No. of patients (*n* = 60) using ≥ 1 drug from class (%)
Cardiovascular	
Bèta blockers	39 (65)
RAAS-inhibitors	34 (57)
Calcium channel blockers	22 (37)
Loop or thiazide diuretics	22 (37)
Gastrointestinal	
Proton pump inhibitors	48 (80)
Antiemetics	32 (53)
Laxatives	24 (40)
Dyslipidemic	
Statins	36 (60)
Pain management	
Acetaminophen	20 (33)
Strong opioids, short-acting	13 (22)
Strong opioids, long-acting	11 (18)
Antiplatelet/anticoagulant	
Platelet aggregation inhibitors	22 (37)
LMWH	10 (17)
Bone metabolism	
Colecalciferol	19 (32)
Zoledronic acid	11 (18)
Antimicrobial	
Antibacterials	15 (25)
Antivirals	14 (23)
Diabetes	
Metformin	11 (18)
Vitamins (excl. colecalciferol)	
Folic acid	11 (18)
Urogenital	
Alpha blockers	10 (17)

depicted in Table 1. The population consisted primarily of men (73%, *n* = 44) and the mean age was 74 years. Despite an age of <65 years, five patients underwent a polypharmacy assessment based on a clear need for polypharmacy consulting or guidance. The mean total number of drugs per patient was 13 (range 6–23), of which two were oncology drugs (range 0–6), two were oncology supportive drugs (range 0–7) and nine were other chronic drugs (range 4–20). The most commonly used chronic drugs were for the treatment of cardiovascular, lipid and/or gastrointestinal disorders (Table 2).

As illustrated in Table 3, most patients had a comorbidity (ACE-27) score of 2 (40%, *n* = 24). Among the 36 patients who were screened for G8 and ECOG-PS, the majority was classified as vulnerable (72%, *n* = 26) with a performance status of 1 (39%, *n* = 14) or ≥ 2 (44%, *n* = 16).

TABLE 3 Geriatric assessment

Characteristic	No. (%)
G8 (*n* = 36)	
14.5–17 (classified as not vulnerable)	10 (28)
<14.5 (classified as vulnerable)	26 (72)
ECOG PS (*n* = 36)	
0	6 (17)
1	14 (39)
≥2	16 (44)
ACE–27 (*n* = 60)	
0	3 (5.0)
1	19 (32)
2	24 (40)
3	14 (23)

Abbreviations: ACE-27, Adult Comorbidity Evaluation-27; ECOG PS, Eastern Cooperative Oncology Group performance score; G8, Geriatric 8.

3.2 | Optimisation recommendations

In total, 101 potential DRPs were found among 47 of 60 patients (78%), resulting in a mean of 1.7 per patient. As shown in Table 4, the three most commonly found potential DRPs were unnecessary drug therapy (*n* = 39), (potential) adverse effects (*n* = 17) and practical problems/optimisations (*n* = 14).

In total, these potential DRPs led to 85 pharmacotherapeutic optimisation recommendations among 45 of 60 patients (75%), resulting in an average of 1.4 recommendations per patient. The most frequent recommendation was discontinuation of a drug (47%, *n* = 40) followed by replacement of a drug (19%, *n* = 16) or adjustment of dose (18%, *n* = 15). Examples of recommendations are illustrated in Table 5.

3.3 | Follow-up of recommendations

Of the 85 recommendations, 35 (41%) were implemented by the treating physician directly after reviewing and discussing it with the patient. After the median follow-up of 4 months, 32 of the 35 (91%) implemented recommendations were still maintained.

3.4 | Reduction in polypharmacy

For 17 of 60 patients (28%), it was possible to reduce the pill burden for the complete follow-up period. In 12 patients (20%), at least one drug could be discontinued. Reducing the dosing frequency could be accomplished in six patients (10%). An attempt to reduce the pill burden was tried for an additional two patients (3.3%). However, due to symptom recurrence the recommended change had to be reversed.

As is illustrated in Table 4, the number of potential DRPs was reduced from 101 to 60 (41% reduction). The number of patients with

TABLE 4 Potential drug-related problems (DRPs)

	Baseline	After optimisation
Number of patients with at least 1 potential DRP (%)	47 (78)	33 (55)
Number of potential DRPs		
Indication		
Unnecessary drug therapy	39	24
Additional drug therapy required	6	6
Effectiveness		
Ineffective treatment	5	3
Underdosed	2	1
Safety		
(Potentially) adverse drug event	17	12
Clinically relevant contraindications or interactions	12	7
Overdosed	6	3
Drug use		
(Practical) drug use problems/optimisations	14	4
Total	101	60

at least one potential DRP could be reduced from 47 to 33 patients (30% reduction).

3.5 | Geriatric assessment subpopulations

To identify patients most likely to benefit from polypharmacy assessment, the outcomes of the concise geriatric assessment were assessed for possible associations with the occurrence of recommendations. No such subpopulation could be identified at statistical significance, although a trend towards significance (p = .079) was seen for people classified as "vulnerable" with the G8 screening (Table S2).

3.6 | Time investment

The mean time spent per patient is summarised in Table 6. On average, collecting the relevant data took about 15 min, the concise geriatric assessment 10 min, the polypharmacy anamnesis 24 min and the polypharmacy analysis including providing the treatment plan to the treating physician 22 min. In total, the mean duration of a polypharmacy assessment was 71 min.

4 | DISCUSSION

In this study, a pharmacist-led polypharmacy assessment led to the identification and implementation of many possible pharmacotherapeutic optimisations among the majority of older cancer patients. Within this population, there was a high prevalence of patients with at least one potential DRP, which is comparable to previous studies with older cancer patients (around 90%–95%) (Nightingale et al., 2017; Yeoh, Si, & Chew, 2013; Yeoh, Tay, Si, & Chew, 2015). Due to many pharmacotherapeutic recommendations, with OncoSTRIP, it was possible to reduce the total number of potential DRPs and the number of patients with at least one potential DRP.

In comparison, polypharmacy assessment through iMAP resulted in the identification of three potential DRPs per patient on average. Additionally, the total number of DRPs could be reduced by 45.5% and the number of patients with at least one potential DRP by 20.5%. The recommendation acceptance rate was 46% (Nightingale et al., 2017). Thus, despite the identification of a higher number of DRPs per patient, the reductions in DRPs were comparable between iMAP and OncoSTRIP. Cumulatively, OncoSTRIP and iMAP provide reproducible and encouraging results that support routine implementation of polypharmacy assessment in this population.

It is anticipated that a recommendation suggested or discussed by a large team, as used in iMAP, is more likely to be adapted than a recommendation suggested by one clinical pharmacist. However, with respect to the comparable acceptance rates of OncoSTRIP and iMAP, no clear preference exists between the two methods. In our view, reporting recommendations directly in the patients' electronic medical records is efficient, especially since the majority of recommendations do not require immediate action. Discussing polypharmacy recommendations in a multidisciplinary team could be beneficial in selected patients.

In this study, we did not record the reasons why prescribers may have chosen not to follow a recommendation. However, the suboptimal acceptance rate in our study can be partly explained by the observation that approximately one-third of all suggested recommendations were conditional ("if life expectancy is estimated below 2 years, than…"), as the pharmacist generally did not know the estimated life expectancy at the time of providing recommendations. It is likely that for some patients the life expectancy was higher than the prerequisite for the recommendation, thereby making it irrelevant.

Pill reduction can decrease the risk of adverse drug events and medication errors, and positively influence compliance by simplifying intake regimens. Pill reduction was accomplished and maintained in a substantial part of patients. Undoing a pill reduction due to symptom recurrence was minimal, suggesting it is feasible for patients to stop the discontinued drug(s) for a longer period.

An important priority of OncoSTRIP was the discontinuation of potentially unnecessary medications with respect to a limited life expectancy, since a large proportion of our population received palliative treatment for an incurable malignancy. This is reflected by the high percentage of recommendations to discontinue a drug. As far as we know, little explicit and practical guidelines exist that aid in the process of deprescribing when a patient's life expectancy is limited. We composed a list of drugs in which, depending on the scenario, deprescribing should be considered. Since discontinuation trials are scarce, the scenarios and proposed cut-off values are mostly based on two studies (Lindsay et al., 2015; Potter et al., 2016) and

TABLE 5 Pharmacotherapeutic recommendations

Recommended optimisation	No. (%)	Examples
Discontinue drug	40 (47)	• Preventive medication in case of a reduced life expectancy (e.g. statins, antihypertensive drugs) • Irrelevant indication (e.g. clopidogrel >1 year after placing of a stent) • Ineffectiveness (tamsulosin, fexofenadine)
Replace drug for better alternative	16 (19)	• Adverse drug reaction (e.g. dexamethasone and hiccups, simvastatin and reflux, metformin and diarrhoea) • Contraindication, for example due to renal dysfunction (e.g. barnidipine) • Newer guidelines (e.g. switch acetylsalicylic acid + dipyridamole to clopidogrel for the treatment of a TIA/CVA)
Adjust dose	15 (18)	• Reducing dose due to renal dysfunction (e.g. pramipexole) or reduced body weight (e.g. LMWH) • Unnecessary or inadequate high dose (e.g. high dose of proton pump inhibitor solely for the purpose of gastric prophylaxis) • Interaction (e.g. increasing dose omeprazole due to use of enzalutamide)
Start drug	5 (6)	• Use of laxative with concurrent use of opioids • Basic dermal product for the treatment of a rash
Other	9 (10)	• Monitoring of certain parameters (e.g. QTc interval, lipids) • Reducing the number of different types of inhalators • Switching from two separate preparations to one combination preparation • Clarifying discrepancies between presumed use and actual use of drugs by patient
Total	85	

TABLE 6 Time investment

Polypharmacy assessment phase	Mean time spent per patient in min (range)
Preparation, collecting relevant data (n = 60)	15 (5–30)
Geriatric assessment (n = 34)	10 (10–10)
Polypharmacy anamnesis (n = 60)	24 (10–45)
Polypharmacy analysis and providing treatment plan to oncologist/haematologist (n = 60)	22 (5–50)
Total	71 (40–120)

on the opinion of experts in the field of oncology and/or geriatrics. However, to strengthen the evidence for deprescribing the listed drugs, more discontinuation trials that evaluate safety of deprescribing are greatly needed.

Time is an essential aspect for successful implementation of a new method. To the best of our knowledge, no studies have analysed the total time investment of polypharmacy assessments among older cancer patients. Nightingale and colleagues reported a mean time investment of the pharmacist-patient session of 22 min (Nightingale et al., 2017), which was comparable to our pharmacist-patient sessions. Studies among the general geriatric population have reported ranges of 20–140 min per individual medication assessment (Gillespie et al., 2009; Lenander, Elfsson, Danielsson, Midlöv, & Hasselström, 2014; Zermansky et al., 2002). With a mean total time of 71 min per polypharmacy assessment, OncoSTRIP is comparable to this reported range. In our community-based hospital, considering a mean of one to two eligible patients per week, it was possible to perform the individual tasks of OncoSTRIP within the routine working day of the involved healthcare professionals.

This study has several limitations. Firstly, this study analysed only a small number of patients of one ambulatory oncology/haematology unit. Furthermore, although a trend towards significance was seen for the association between the G8 screening and the occurrence of recommendations, due to the limited numbers of screenings, the study was not powered adequately to identify a subpopulation

that would especially benefit from an OncoSTRIP polypharmacy assessment. Future research should examine the possibility of possible subpopulations. Finally, with the exploratory design, we did not evaluate the effect of OncoSTRIP polypharmacy assessments on (long-term) patient outcomes such as increase in quality of life and decrease in adverse drug events, toxicity, hospitalisations and associated costs.

In conclusion, the OncoSTRIP polypharmacy assessment resulted in the identification of a high number of possible pharmacotherapeutic optimisations among older cancer patients. An essential aspect for this specific population is to consider the changed goals of care with respect to a reduced life expectancy. OncoSTRIP made it possible to integrate polypharmacy assessments into routine care of this population. Future studies are needed to identify possible high-risk subpopulations and to assess the effects of OncoSTRIP polypharmacy assessments on (long-term) patients' outcomes.

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CONFLICT OF INTEREST

None to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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