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Published in:
International Journal of Clinical Pharmacy

DOI:
10.1007/s11096-012-9747-7

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2013

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Bulsink, A., Imholz, A. L. T., Brouwers, J. R. B. J., & Jansman, F. G. A. (2013). Characteristics of potential drug-related problems among oncology patients. International Journal of Clinical Pharmacy, 35(3), 401-407. DOI: 10.1007/s11096-012-9747-7

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Download date: 11-02-2018

Int J Clin Pharm (2013) 35:401–407
DOI 10.1007/s11096-012-9747-7

RESEARCH ARTICLE

Characteristics of potential drug-related problems among oncology patients

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Received: 10 February 2012 / Accepted: 18 December 2012 / Published online: 3 January 2013
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Abstract *Background* Oncology patients are more at risk for drug related problems because of treatment with (combinations of) anticancer drugs, as they have a higher risk for organ failure or altered metabolism with progression of their disease. *Objective* The aim of this study was to characterize and to evaluate the frequency of potential drug related problems (pDRPs) among oncology patients. *Setting* Outpatient- and day-care centres for Internal and Pulmonary Medicine at the Deventer Hospital, Deventer, The Netherlands. *Method* A prospective, descriptive, observational study was carried out from March 2010 to March 2011 at the Deventer Hospital, Deventer, The Netherlands. All patients older than 18 years receiving anticancer drugs prescribed by an internal medicineoncologist or pulmonologist-oncologist were included. *Main outcome measure* The primary outcome was the number and type of pDRPs according to Dutch guidelines. *Results* Among 546 patients with cancer, 952 pDRPs were identified, of which 474 were oncology-related. These were mainly drug interactions (IA) (246 IA in 157 patients) and potential contraindications (pCI) (201 pCI in 143 patients). *Conclusion* Most identified pDRPs in cancer patients were IAs and pCIs and involved corticosteroids. The most frequently occurring oncology-related IAs were classified as minor or moderate levels of severity.

Keywords Contraindications · Drug-drug interactions · Drug-related problems · Oncology · The Netherlands

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Impact of findings on practice

- Oncology patients are at high risk for drug-related problems and therefore need intensive medication monitoring and counselling.
- The management of cancer is multi-disciplinary. This can lead to errors in medication information, transfer and unnoticed potential drug-related problems (pDRPs). Therefore an actual and accurate patient-verified list of current medications is a major element in identifying pDRPs.
- Most of the commonly occurring pDRPs are contraindications (CI) and drug-interactions (IA), mostly involving corticosteroids.

Introduction

The incidence of cancer has increased over time. In the Netherlands during 2010, 95,456 new cases of cancer were identified, an increase of 3.3 % compared with 2009 and of about 35 % compared with 2000. Of the newly identified cases in 2010, 42 % were between 60 and 75 years of age and 31 % over 75 years [1].

For several reasons, oncology patients in particular need intensive medication monitoring and counselling. First, elderly patients often use more drugs as a result of comorbidities. This increases the risk of drug-related problems with anticancer drugs in these patients. The use of anticancer drugs often results in the use of other agents to reduce or prevent side-effects of the anticancer treatment, thereby increasing the interaction potential [2]. Furthermore, cancer itself increases the need for more medications. Cytotoxic agents have a narrow therapeutic window and a complex pharmacologic profile. In oncology patients, pharmacokinetic parameters can be altered by the disease itself or due to malnutrition, reduced levels of serum-binding proteins, oedema, or hepatic and/or renal dysfunction [3]. Patients with cancer are therefore more at risk for drug interactions. It has been shown that 20–30 % of adverse drug reactions can be attributed to drug interactions [2]. Oncology-related PDIs involve between 18 and 58 % of cancer patients [3–5].

The management of cancer is multi-disciplinary. In The Netherlands, pharmaceutical care for cancer patients is mostly divided into two channels. Monitoring and dispensing of supportive care agents is performed by the community pharmacist, generally outside the range of the hospital, whereas most anticancer drugs, except for oral formulations, are prepared at the Department of Clinical Pharmacy and administered on an oncology ward of a hospital. This can lead to errors in medication information transfer and unnoticed drug-related problems (DRPs). Therefore an actual and accurate list of current medications is a major element in identifying potential DRPs.

Aim of the study

The aim of this study was to characterize and to evaluate the frequency of potential drug-related problems (pDRPs) among oncology patients.

Method

Setting and patients

This prospective, descriptive, observational study was carried out from March 2010 through March 2011 at the Deventer Hospital, Deventer, The Netherlands. The Deventer Hospital is a teaching hospital (405 clinical beds) located in the eastern region of The Netherlands. The hospital serves a catchment population of about 180,000 residents.

Included were patients older than 18 years receiving anticancer drugs, including cytotoxic agents, hormones and biologicals, which were prescribed by a medical oncologist or pulmonologist-oncologist. Participants were recruited to the study through an intake appointment with a nurse oncology consultant. Intake with the nurse oncology consultant took place when a patient was diagnosed with (relapsed) cancer and could be considered for anticancer drugs therapy, or prior to change of anticancer drug treatment regimen due to progression. In 2009, 558 oncology patients had a first appointment with the nurse oncology consultant prior to treatment with anticancer agents or before change of treatment regimen.

Patients were excluded from the study if they received no anticancer drug therapy after intake. Patients gave written informed consent at the interview or with a returned list. A declaration of no objection was issued by the Dutch Central Committee on Research Involving Human Subjects accredited Medical Ethical Review Board of the Isala Clinics Zwolle, The Netherlands.

Data collection

All included patients received standard pharmaceutical care according to Dutch regulatory requirements [6]. For all patients, on intake with the nurse oncology consultant, a list of current medications, based on the drug dispensing history records of the community pharmacy, was made up and analysed by a pharmacist. The list of current medications, including identified pDRPs, was provided to the treating medical oncologist or pulmonologist-oncologist. Follow-up to identified problems was not part of this study.

Before the intake-appointment with the nurse oncology consultant, all patients, with the exception of those treated for lung cancer, received a written invitation for voluntary participation in a medication reconciliation interview with a pharmacist. They were asked to send in a self-made list of current medications by filling out an enclosed blank medication list. Patients treated for lung cancer were excluded from the medication reconciliation interview at the request of the pulmonologist, because of their poor prognosis. Patient characteristics, data on disease and treatment and laboratory data were obtained from the medical records database of the hospital. Comorbidities were classified according to International Statistical Classification of Diseases and Related Health Problems 10th Revision [7].

Classification of DRPs

The potential DRPs in this study were analysed according to the Shumock-algorithm [8]. Identified potential DRPs were classified as presented earlier by van den Bemt et al. [9]. The items categorized as "therapeutic errors" were considered to be potential DRPs. Oncology-related drug–drug interactions were assessed according to the consensus

of the Dutch multidisciplinary national expert group on interactions in oncology [10]. Other drug assessments were made according to the Dutch National Drug Database (G-standard) [11]. Both quantify the strength of scientific evidence ("*no evidence*" through 4 "*controlled, published interaction studies*") and clinical significance (A "*Clinically irrelevant effect*" through F "*Death*") according to the same classification system of 6 severity levels [12].

Statistical analysis

Data were collected with the use of MS Excel 2003 and analysed with the use of MS Access 2003. Each consultation was considered to be a unique unlinked participant. Descriptive statistics were used to describe patient characteristics, frequency, type and classification of pDRPs.

Results

Patient characteristics

From March 2010 to March 2011, a total of 577 intake-appointments with 541 patients were made with the nurse oncology consultant. The inclusion of patients is shown in Fig. 1. There were 87 intakes with 81 patients who were diagnosed with lung cancer. At the request of the pulmonologist, patients treated for lung cancer were not invited to participate in a medication reconciliation interview and their medications were analysed based on DDHRs alone. For a total of 392 intakes, patients were reminded to return their medication list by mail, and 201 (51.3 %) of these responded. The overall number of intakes per patient was 1.07 (range 1.00–1.08) times. The number of intakes with the nurse oncology consultant and the number of patients are considered equal and will further on be referred to as patients. The patient characteristics are shown in Table 1.

Drug-related problems

A total of 4,618 medication prescriptions were analysed in which 952 DRPs were identified in 546 patients, including patients treated for lung cancer, of which 474 (49.8 %) DRPs were oncology-related. For each patient the best fitting list of currently used medications was used for analysis. The identified DRPs are shown in Table 2. The oncology-related DRPs that we detected were about equally divided over the categories "contraindication" (CI) and "interaction" (IA). There were 201 oncology-related CIs identified in 143 patients in a group of 546 (26.2 %) patients: 25 CIs could be attributed to an anticancer drug and 176 to a supportive care agent. There were 246 oncology-related IAs identified at least once in 157 patients in a group of 546 (28.8 %) patients, of which 26 were IAs between drugs of the same anticancer drug treatment regime. Ninety-four IAs could be attributed to an anticancer drug and 152 to a supportive care agent. In 70.4 % of the cases, oncology-related double medication included drugs that were part of the chemotherapy regimen, such as dexamethasone and prednisone. Other classified double medications included paracetamol (acetaminophen) and omeprazole. The items for the DRP categories CI and IA are shown in Tables 3 and 4.

Of the 201 oncology-related CIs, 25 (12.4 %) were a CI for an anticancer drug and 176 (87.6 %) were a CI for oncology-related supportive care. The three most identified oncology-related CIs were hypertension (46.3 %), diabetes mellitus (22.4 %) and peptic ulcer (6.7 %). All were CIs

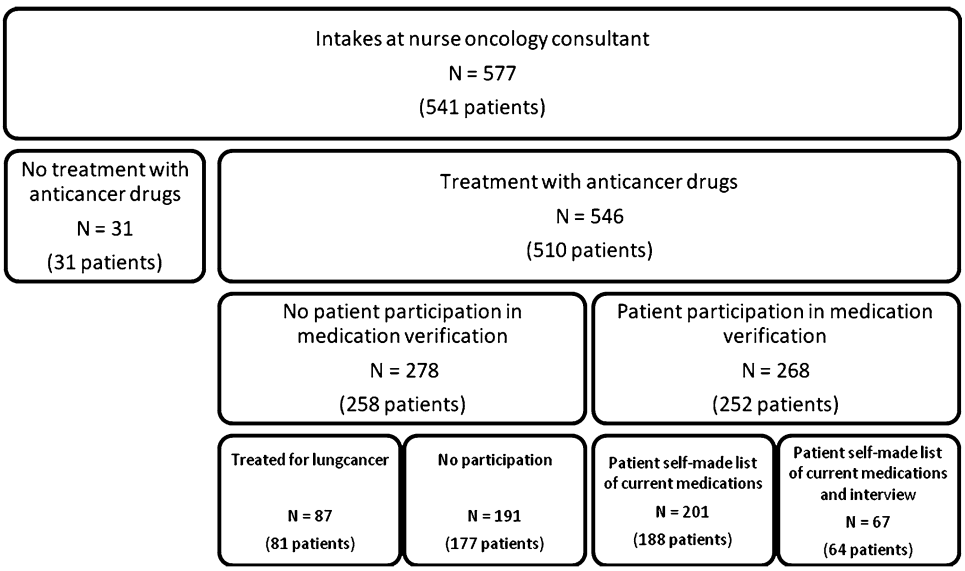

Fig. 1 Patient inclusion. *N* number of intakes

Table 1 Characteristics of patients in the study

Inclusion	
Number of patients	510
Number of intake appointments	546
1	477
2	60
3	9
Intakes per patient	1.07
Sex	
Male	238 (43.6 %)
Female	308 (56.4 %)
Age in years	
Mean ± SD	63.7 ± 12.0
Type of cancer	
1. Gastrointestinal	172 (31.5 %)
2. Breast	146 (26.7 %)
3. Haematological	62 (11.4 %)
4. Lung	87 (15.9 %)
5. Urologic	36 (6.6 %)
6. Other	43 (7.9 %)
Treatment intent	
Curative/adjuvant	248 (45.4 %)
Palliative	298 (54.6 %)
Cancer treatment	
Chemotherapy	408 (74.7 %)
Hormonal therapy	1 (0.2 %)
Molecular therapy	42 (7.7 %)
Combinations	95 (17.4 %)
Drugs	
MOs × total	4,618
Mean no. of drugs ± SD	8.5 ± 3.7
MOs oncolytics	1154 (25.0 %)
Mean no. of oncolytics ± SD	2.1 ± 0.9
MOs supportive care drugs	897 (19.3 %)
Mean no. of supportive care drugs ± SD	1.6 ± 1.0
MOs other drugs	2573 (55.7 %)
Mean no. of other drugs ± SD	4.7 ± 3.4
Follow-up (3 months)	
Died	52 (9.5 %)

MOs medication orders

Table 2 Analysed DRPs among cancer patients

Oncology related DRPs	474
Contraindication	201 (42.4 %)
Contraindication per patient ± SD	0.4 ± 0.7
Patients with ≥1 contraindication	143 (26.2 %)
Interaction	246 (51.9 %)
Interaction per patient ± SD	0.5 ± 0.9
Patients with ≥1 interaction	157 (28.8 %)
Unjustified mono-therapy	0 (0.0 %)
Double medication	27 (5.7 %)
Other DRPs	478
Contraindication	246 (51.5 %)
Contraindication per patient ± SD	0.5 ± 1.1
Patients with ≥1 contraindication	117 (21.4 %)
Interaction	177 (37.0 %)
Interaction per patient ± SD	0.3 ± 0.9
Patients with ≥1 interaction	100 (18.3 %)
Unjustified mono-therapy	2 (0.4 %)
Double medication	53 (11.1 %)

with corticosteroids for supportive care. The most identified CIs for other agents were diabetes mellitus (30.5 %) and hypertension (16.7 %).

Of the 246 oncology-related IAs, 94 (38.2 %) involved at least one anticancer drug and 152 (61.8 %) a supportive care agent. In 56 (22.8 %) of the oncology-related IAs, coumarins were involved. Coumarins were also involved in the interaction with the highest level of severity (category F), an IA with tamoxifen. For the IAs with a supportive care agent, 65.1 % could be attributed to NSAIDs in combination with a corticosteroid and 28.3 % to simvastatin in combination with a corticosteroid.

For IAs with an antineoplastic agent, 79 IAs (84.0 %) were classified as minor (A and B), 11 IA (11.7 %) as moderate (D) and 4 IAs (4.3 %) as major (E and F). For IAs with a supportive care agent, 43 IAs (28.3 %) were classified as minor (B) and 107 IAs (70.4 %) as moderate (C and D).

The interacting agents dexamethasone in the IA with irinotecan or protein kinase inhibitors, both classified as 3A, were part of the anticancer treatment and was considered to be an intended IA. The IA of the supportive care drug prednisolone with dexamethasone, classified as 3D, was an IA between agents that were part of the anticancer treatment as well. IAs between other drugs in cancer patients could mainly be attributed to the IA between a renin-angiotensin system (RAAS) inhibitor and a diuretic (17.5 %) and between a RAAS-inhibitor and an NSAID (8.5 %).

Discussion

In this study, most CIs with an anticancer drug involved fluoropyrimidines and most CIs with a supportive care agent involved corticosteroids. However, all CIs, i.e. comorbidities, were adequately managed, and, as a consequence, were not considered to be of clinical relevance. Most IAs related to the use of supportive care drugs were classified as moderate (70.4 %). The most frequently identified IA with a supportive care drug was a

Table 3 Contraindications involving anticancer, supportive and other agents

Agent	Contraindication	Effect	n
Anticancer agent			
Fluoropyrimidines	Angina pectoris	Capecitabine, fluorouracil and tegafur can trigger attacks of angina pectoris	5
Capecitabine	Decreased renal function	Increased level of capecitabine	5
Carboplatin	Decreased renal function	Increased level of carboplatine	4
Rituximab	Heart failure	Increase of heart failure	3
Cyclophosphamide/Iphosphamide	Heart failure	Increase of heart failure	2
Anthracycline derivates	Heart failure	Increase of heart failure	2
Cisplatin	Decreased renal function	Nephrotoxic	1
Capecitabine	Liver function disorder	Increased serum level of capecitabine	1
Epirubicin	Liver function disorder	Increased serum level of epirubicin	1
Etoposide	Decreased renal function	Increased serum level of etoposide	1
Supportive care agent			
Corticosteroid	Hypertension	Corticosteroids can induce hypertension[a]	93
Glucocorticosteroid	Diabetes Mellitus	Increased level of serum glucose	45
Glucocorticosteroid	Peptic Ulcer	Glucocorticosteroids can induce an ulcus pepticum	14
Corticosteroid	Depression	Corticosteroids can induce and increase depression[b]	11
Metoclopramide	Decreased renal function	Increased level of serum metoclopramide	5
Corticosteroid	Psoriasis	Psoriasis can aggravate after stop with corticosteroid	5
Glucocorticosteroid	Glaucoma	Glucocorticosteroids can induce glaucoma	2
Metoclopramide	Epilepsy	Metoclopramide can trigger an epileptic attack	1
Other agent[c]			
RAAS-inhibitor	Diabetes mellitus	Decreased serum glucose level	28
Selective beta blocker	Diabetes mellitus	Cover symptoms of low serum glucose level and inhibit recovery	26
Antithrombotic	Hypertension	Increased risk of cerebral haemorrhage	23
Selective beta blocker	Asthma/COPD	Bronchoconstriction at higher dose	13
Thiazides	Diabetes mellitus	Increased level of serum glucose	10
Opioids	Asthma/COPD	Dose-dependent breath reduction	9
Loop diuretic/thiazides	Gout	Increase of gout attack	7
Salicylates	Peptic Ulcer	Increased risk of peptic ulcer	7
Loop diuretic	Hyperplasia of prostate	Acute urine retention	7
Opioids	Hyperplasia of prostate	Urine retention	7

[a] Especially at high doses (≥20 mg prednisone/day and equivalent doses)

[b] Especially at high doses (≥40 mg prednisone/day and equivalent doses)

[c] For other agents the 10 most frequently identified CI are reported

corticosteroid with a NSAID (65.1 %). However, in 68 of the 99 (68.7 %) cases, a proton pump inhibitor was already prescribed, a required action to reduce the risk of peptic ulcer, or the use of the NSAID was not chronic.

Although there are methodological differences, the five most identified oncology-related IAs by this study are in agreement with those identified by Riechelmann et al. [3] as well as those identified by Van Leeuwen et al. [5]. Our study results are dissimilar to those of Voll et al. [4], because of a high percentage of antiretroviral drugs prescriptions in their patients, causing specific IAs. Both Riechelmann et al. and Van Leeuwen et al. used The Drug Interactions Facts [13] as a drug-interaction-database whereas in this study the Dutch national drug database [11], including the consensus-based management of anticancer drug interactions, was used [10]. Van Leeuwen et al. found a higher percentage of patients with IAs with anticancer drugs: 138 IAs occurring at least once in 161 patients in a group of 278 (58 %) patients. This is mainly due to the inclusion of IAs (classified by the authors as major) with potential QT-interval prolongation and/or *torsades de pointes*-inducing properties according to the

Table 4 Interactions involving anticancer and supportive agents

Agent	Interacting agent	Effect	Class[a]	n
Anticancer agent				
Cytostatic agent	Coumarins	Altered coagulation time	1B	56
Irinotecan[b]	Dexamethasone	Decreased serum level of irinotecan	3A	15
PKI	Dexamethasone	Decreased serum level of PKI	3A	4
Various[c]	Valproic acid	Therapeutic failure of valproic acid	2D	4
Methotrexate	NSAID	Increased serum level of methotrexate	3E	3
Methotrexate/etoposide/ teniposide	Carbamazepine/phenytoin/ phenobarbital	Therapeutic failure of anti-epileptic drug	2D	3
PKI	Secretion inhibitor	Decrease of bioavailability of PKI	1A	3
Various[c]	Phenytoin	Therapeutic failure of phenytoin	3D	2
Various[c]	Carbamazepine	Therapeutic failure of carbamazepine	2D	2
Tamoxifen	Coumarins	Increased coagulation time	1F	1
Imatinib	Statin	Increased risk of myopathy	3A	1
Supportive care agent				
Corticosteroid	NSAID (excl. COXIB)	Increased risk of peptic ulcer	3C	99
Dexamethasone	Simvastatin/atorvastatin	Decreased serum level of simvastatin, atorvastatin and active metabolites	3B	43
Dexamethasone	Prednisolone	Decreased serum level of dexamethasone	3D	7
Aprepitant	Coumarins	Coagulation time decreases	–	2
Antiemetic	Ropinirole	Counteracting effect	2D	1
Other agents[d]				
RAAS-inhibitor	Diuretic	Once only sudden decrease of blood pressure when RAAS-inhibitor is added to diuretic	3D	31
RAAS-inhibitor	NSAID	Decreased action of RAAS-inhibitor	3D	15
Beta blocker	NSAID	Decreased action of beta blocker	3C	15
Alpha blocker	Beta blocker/calcium antagonist	Once only sudden decrease of blood pressure when alpha blocker is added to beta blocker/calcium antagonist	3B	14
Beta blocker	Oral antidiabetic	Increased effect of hypoglycaemia and inhibit recovery	3B	14
Beta blocker selective	Insulin	Increased effect of hypoglycaemia and inhibit recovery	3B	11
Diuretic	NSAID	Therapeutic failure of diuretic	3D	10
Coumarin	(Es)omeprazol	Increased effect of coumarin	1D	9
Bisphosphonate	Antacid/iron/calcium	Decreased absorption of bisphosphonate at simultaneous intake	0A	7
Salicylate (antithrombotic)	NSAID (excl. ibuprofen)	Increased risk of bleeding ulcer	3C	5

COXIB cyclo-oxygenase-2 inhibitor, *PKI* protein kinase inhibitor

[a] Classification of levels of severity and evidence by documentation of oncology related drug interactions [13]

[b] Combination of irinothecan and dexamethasone within the same treatment protocol is regarded as an intended drug interaction. All reported IA are the result of intended combination within the treatment protocol

[c] Cisplatin, cyclophosphamide, doxorubicin, etoposide, iphosphamide, methotrexate, paclitaxel

[d] For other agents the 10 most frequently identified CI are reported

Arizona-list [14]. These QT IAs in the study by Van Leeuwen are responsible for almost one-third of the IAs found.

On behalf of the pulmonologist, patients treated for lung cancer were not invited for voluntary participation. The number of patients treated for lung cancer in this study, about 15 %, is substantial. In general, patients treated for lung cancer are more ill and have a worse prognosis as compared with breast and/or colon cancer (the two most commonly occurring types of cancer). In our opinion, patients treated for lung cancer should therefore not be excluded from the descriptive analysis of occurring pDRPs despite the fact that their medications were analysed only based on DDHRs.

Conclusion

We showed a high prevalence of identified oncology-related DRPs in cancer patients. The DRPs involved are mainly contraindications (CIs) and drug interactions (IAs). There were 201 oncology-related CIs identified in 143 patients in a group of 546 (26.2 %) patients: 25 CIs could be attributed to an anticancer drug and 176 to a supportive care agent. Most CI with an anticancer drug involved fluoropyrimidines and most CIs with a supportive care agent involved corticosteroids. There were 246 oncology-related IAs identified at least once in 157 patients in a group of 546 (28.8 %) patients, of which 26 were IAs between drugs of the same anticancer drug treatment. For IAs with an antineoplastic agent, 79 IAs (84.0 %) were classified as minor (A and B), 11 IAs (11.7 %) as moderate (D), and 4 IAs (4.3 %) as major (E and F). For IAs with a supportive care agent, 43 IAs (28.3 %) were classified as minor (B) and 107 IAs (70.4 %) as moderate (C and D).

Commonly occurring pDRPs are CIs and IAs, mostly involving corticosteroids, and are of a minor or moderate level of clinical significance.

Acknowledgments The authors are grateful for the substantial contributions to this study of G.J. Altena, G.J. Borst, S.D. Boor and F. Karabulut, MSc students in pharmaceutical sciences, M.M. Voogel-Fuchs, staff member oncology, and of M.E.L. Arbouw, PharmD, PhD, Deventer Hospital, Deventer.

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of interest No conflicts of interest to declare.

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