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Abstract

Objectives

Most patients receive systemic anti-cancer therapy (SACT) as day cases and toxicities, if they occur, are likely to appear first in primary care. Pharmaceutical care can be delivered by community pharmacists, but little is known about the epidemiology of SACT toxicities in the community and potential interventions to address these which raises the questions: what are the typology of SACT-associated toxicities experienced by community based patients and what are the associated pharmaceutical care issues (PCIs)? The aim of this study was to identify toxicities and pharmaceutical care issues of patients prescribed SACT for lung cancer and understand the potential for community pharmacists to deliver aspects of cancer care including toxicity management.

Methods

Retrospective analysis of clinical records of patients prescribed oral and parenteral SACT to describe: patient characteristics; SACT toxicity; PCIs; and episodes of unscheduled care.

Key findings

Twelve categories of toxicity and thirteen categories of PCIs were identified from 50 patients. More PCIs were observed with oral SACT/oral-parenteral combinations than with parenteral regimens. PCIs which could be managed by community pharmacists were mucositis; skin toxicity; gastrointestinal toxicity; reinforcing patient education; and identification/prevention of drug interactions.

Conclusions

Community pharmacists are ideally placed to provide pharmaceutical care to patients with lung cancer prescribed SACT. Cancer specialists in secondary care can signpost patients to community pharmacists for early management of simple toxicity.

Introduction

Lung cancer is the most common cause of cancer deaths worldwide resulting in 1.59 million deaths in 2012.[1] The risk of developing lung cancer increases with age and as the median age at diagnosis is 70 years old, this population is a group of mostly elderly patients who have multiple co-morbidities making them increasingly susceptible to treatment related toxicity. Most patients present with locally advanced or metastatic disease. Patients with advanced disease who are considered fit enough (Performance Status 0 – 2) are offered palliative systemic anticancer therapy (SACT) or palliative radiotherapy to improve symptoms and increase overall survival.[2] In the United Kingdom (UK) approximately 58% of patients with lung cancer receive SACT.[3] Careful monitoring and early intervention of treatment associated toxicity is recommended.[4]

In the UK, most patients with lung cancer receive SACT as hospital out-patients, returning every 2-3 weeks for treatment. In the intervening period, these patients are at home. Cancer care clinical pharmacists are integrated into multidisciplinary teams (MDTs) and are involved in treatment decisions and ongoing therapy management. . SACT prescriptions are verified by a cancer care pharmacist prior to dispensing and this affords multiple opportunities for pharmacist's interventions, such as toxicity assessment, patient counselling and education. An increasing number of cancer care pharmacists also prescribe SACT and manage their own caseload of patients at hospital out-patient clinics.[8] Pharmacist's contributions to patient care are recorded as pharmaceutical care issues (PCIs). In Scotland, a national standardised cancer pharmaceutical care plan has been in use for over 15 years. This document is used by hospital cancer care pharmacists in either paper or electronic form. The care plan was introduced to standardise pharmaceutical care and to capture data to facilitate categorisation of SACT toxicity and associated PCIs.

At the time this study was conducted, the two most commonly used anticancer agents for lung cancer were carboplatin and cisplatin. Immunotherapy was not available commercially for patients in Scotland with lung cancer and tyrosine kinase inhibitors were recommended but with some restrictions on prescribing. SACT related toxicity generally manifests whilst patients are at home.

Patients are educated to contact a healthcare professional if they become unwell and some patients carry a hand-held booklet containing abbreviated information about their cancer treatment. . It is advisable that both patients and primary care teams are aware of possible problems; the action to take in the event of a toxicity; and the urgency of an intervention. Patients are signposted by the hospital cancer team to their general practitioner (GP), a cancer telephone helpline or out-of-hours emergency services according to the severity of the toxicity. Early recognition of red flag symptoms such as a raised temperature following SACT, offers an opportunity for collaborative, preventative action. Severe toxicities can contribute to hospital admissions.[6] Community pharmacists are an underutilised source of expertise in primary care and could support patients receiving SACT. Todd et al showed that 89% of the population can walk to a community pharmacy within 20 minutes which makes community pharmacists more accessible to most patients than their cancer hospital. [Todd] However, although SACT improves overall survival in patients with advanced lung cancer, further research on toxicities and adverse events experienced whilst the patient is resident in primary care is needed. [7]

Community pharmacists are readily accessible and are ideally placed to support patients to self-manage some toxicity and detect early signs of more complex red flag symptoms where medical intervention is recommended. Strategic policy recommends collaborative pharmaceutical care in Scotland with community-based services arranged around patients.[9]

There are few data describing PCIs or community based pharmacists' interventions for a community based cohort with lung cancer. To inform pharmaceutical care in primary and secondary care, identification of the toxicities experienced by patients with lung cancer, and consideration of potential care issues, is required. This study was conducted to identify toxicities and PCIs of patients prescribed SACT for lung cancer and understand the potential for community pharmacists to deliver aspects of cancer care including toxicity management.

Methods

The study was a descriptive retrospective analysis of lung cancer SACT-associated PCIs and toxicity experienced by patients attending the New Victoria Hospital in Glasgow, Scotland.

Fifty patients prescribed commercially available SACT were included in the study. This represented approximately 50% of the annual patient throughput gaving a wide representation of prescribed regimens. NHS information governance processes were applied in data handling, collection and storage. Ethical approval was not required.

A high-level description of the patient pathway was thus:

1. Patient attends clinic and has bloods taken for biochemistry and haematology
2. Patient is assessed by a prescriber for continuation of SACT if appropriate
3. SACT is prescribed on the electronic SACT portal (Chemocare®)
4. Cancer care pharmacist verifies prescription; updates e-care plan
5. Patient collects oral SACT from the hospital pharmacy and returns home or,
6. Patient returns the following day to receive parenteral SACT
7. Patient returns in 1,2- or 3-weeks time according to regimen treatment interval

Data were collected from existing sources: the Electronic Patient medical Record (EPR, a web-based clinical record), the electronic pharmaceutical care plan (completed by cancer care pharmacists and stored in the EPR) and Chemocare®. Patient demographics, toxicity and unscheduled care data were obtained from the EPR. An episode of unscheduled care was an unplanned admission to the Accident and Emergency Department in the patient's local hospital. PCIs were obtained by interrogating the electronic pharmaceutical care plan. Care plans were updated in real time by cancer care pharmacists during their attendance at cancer clinics and wards and stored on the Health Board EPR, which was accessible by primary care clinicians. At the time of this study, community pharmacists did not have access to EPR.

Demographic data collected were: age; type of lung cancer; baseline weight; gender; smoking status; performance status at diagnosis; baseline renal function as eGFR; and any recorded co-morbidities which were classified according to body system.

SACT data collected were name of regimen; line of treatment; toxicity, graded 0-4 by the patient's clinician; and the number of PCIs by regimen.

Results

The key patient characteristics are shown in Table 1. Most patients were female, and the median age was 66 years. Sixty percent of patients had NSCLC.This is in accordance with the Scottish trends in lung cancer incidence.

Ten different SACT regimens were prescribed for first or second-line treatment, Table 2. All the regimens were approved for use in the West of Scotland and were prescribed according to protocol. The regimens included only parenteral SACT, only oral SACT or a parenteral/oral combination. Etoposide was given orally on day 2 in some regimens.

Toxicity was categorised by body system and the gastrointestinal (GI) toxicities were further separated into nausea and vomiting, constipation and diarrhoea. Toxicity was recorded by hospital prescribers in their clinic letters but was infrequently graded according to the international Common Toxicity Criteria. Prescribers documented twelve different categories of toxicity and 83 episodes of toxicity, Table 3. Thirty seven patients (74%) experienced at least one episode of toxicity. Fifteen patients (30%) reported two or more toxicities. Thirteen patients (26%) reported no toxicity, of whom, four (31%) completed the planned number of cycles and five patients received only one SACT cycle.

A total of 60 PCIs were recorded in the study sample's pharmaceutical care plans. More PCIs were identified when there was oral SACT included in the regimen; 20 for only parenteral regimens and 40 for only oral and parenteral/oral combination regimens. Two oral SACT regimens were prescribed, erlotinib (n=6, 16 PCIs) and topotecan (n=1, zero PCIs). PCIs were grouped by body system or medicines problems according to the SACT regimen (Table 4). The average number of PCIs per patient was greater for the regimens with oral SACT, Table 5. The PCIs most commonly recorded with oral SACT in the regimen were GI (n=13), rash (n=6) and patient education (n=5).
Eighteen patients (36%) had one or more episodes of unscheduled care resulting in admission to hospital which was verified from the admission and discharge dates in the EPR. The range of length of stay was 1 - 23 days, average 5.2 days. The total number of days in hospital was 103 days. Ten admissions (52%) were for infection or sepsis.

Discussion

This study sought to identify the type and number of PCIs and treatment-related toxicity associated with SACT given for lung cancer, and to consider which might be resolved by community pharmacists. Sixty PCIs were identified, GI being the most common and encompassed nausea, vomiting, mucositis, diarrhoea and constipation. Twenty two percent of all toxicity was GI related. Community pharmacists could reinforce patient counselling on how and when to take antiemetics and mouthwashes to maximise their efficacy, and support patients with mild constipation or diarrhoea, being mindful of the need to seek early intervention when diarrhoea quickly progresses beyond 3-4 stools per day.

Of interest, more PCIs were observed when the regimen contained oral SACT (erlotinib, etoposide or vinorelbine). Oral regimens are sometimes perceived to require fewer interventions than parenteral regimens, and it is important to be aware

that the toxicity associated with erlotinb, a tyrosine kinase inhibitor, is significantly different to conventional chemotherapy. Erlotinib was the regimen with the highest number of recorded PCIs being skin rash, GI toxicity and patient education. Erlotinib has significant drug interactions including increased drug clearance in smokers and a reduction in bioavailability when co-administered with drugs that increase gastric pH such as proton pump inhibitors. Given the number and type of PCIs associated with erlotinib, community pharmacists are ideally placed to be the first point of contact for patients who require a pharmaceutical intervention. Community pharmacists have developed relationships with their patients and are accessible without appointments every day. Interventions may include patient education on medicines administration, self management of skin rash and diarrhoea using over-the-counter medicines, and smoking cessation strategies, an area where community pharmacists are trained to offer these services. As a follow up action, the Scottish community pharmacy Minor Ailment Formulary was cross-referenced with the UK Oncology Nurses Society SACT toxicity guidelines, gaps were identified and a request made to add additional medicines to the Glasgow Formulary, thus enabling community pharmacists to provide supportive medicines free of charge and without a prescription.

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Patients prescribed oral SACT were offered education by the hospital cancer care pharmacist and this was recorded as a PCI in the pharmaceutical care plan. This observation was also reported by Watkins who identified counselling patients as a common theme in an evaluation of interventions made by cancer care pharmacists at an English cancer centre. Ref JOPP Hospital pharmacists should consider signposting their patients to community pharmacists for management of simple toxicity with the caveat that the community pharmacists need access to up to date information on SACT treatment protocols and toxicity management algorithms. The community pharmacist is in the enviable position of having access to their patients' medication history and can proactively make an intervention if a drug-drug interaction is identified.

The 10 different SACT regimens prescribed across the study population gave rise to 12 different categories of toxicity and 83 episodes of toxicity. The study was not designed to identify predictive factors for toxicity and patients with lung cancer vary in their disease, co-morbidity and choice of SACT however, the reported toxicity was broadly as expected given the regimens used. The grade of reported toxicity was not identified in this study as few of the prescribers recorded this in their clinic letters. Haematological and renal toxicity were the most common and reflect the use of platinum combination SACT. Fatigue was reported on 10 occasions. While there is limited therapeutic intervention for fatigue, it can significantly affect patient's quality of life and concordance with oral SACT. Cancer charities have patient-friendly advice on dealing with fatigue and community pharmacists could signpost patients to this information.

Of the thirteen patients who reported no toxicity, only four completed the planned number of SACT cycles and five of the thirteen received only one cycle. It is likely

that the absence of toxicity is related to fewer episodes of SACT given to this group of patients. Eighteen patients (36%) had an episode of unscheduled care and were admitted to hospital. The reasons for admission were varied and half were due to infection or sepsis. It is unlikely that any of the admissions could have been prevented, because neutropenia is an unavoidable consequence of cytotoxic chemotherapy.

Two broad areas where patients can be supported by their community pharmacist were identified by Lewis. [Ref PJ] These were "recognise and refer" and "counsel or treat". Recognise and refer included for example, early identification of fever, infection, shortness of breath or uncontrolled diarrhoea where urgent medical intervention is warranted. Counsel or treat includes mouth care, rash management and lifestyle adjustments, among others and supports the hypothesis that community pharmacists can help patients through their cancer treatment journey.

Community pharmacists would need to be supported to provide pharmaceutical care to patients receiving SACT. Undergraduate oncology education is not comprehensive enough to enable community pharmacists to deliver an enhanced role to patients receiving SACT. Abbott *et al* found that a substantial proportion of community pharmacists in Canada lacked understanding of oral SACT and required education and training.[10] Similar findings were reported by O'Bryant *et al* who surveyed community pharmacists in the United States. They found that community pharmacists were most knowledgeable about dosing and least knowledgeable about adverse effects.[11] These barriers can be overcome through sharing of clinical information and SACT treatment protocols which provide advice on common toxicity, drug interactions, monitoring and red flag symptoms. Most community pharmacists in the UK do not have access to hospital electronic records and cancer care pharmaceutical care plans. To safely transfer pharmaceutical care across boundaries from hospitals to primary care, the hospital records need to be accessible by the primary care healthcare professionals, including the SACT treatment protocol. Ideally, community pharmacists would record their interventions on a shared pharmaceutical care plan and work is underway in Greater Glasgow and Clyde Health Board to enable sharing of electronic pharmacy documentation. A pilot of community pharmacist access to the EPR is underway which will enable community pharmacists to read cancer pharmaceutical care plans and will enhance communication across the interface facilitating seamless care. Further work to identify community pharmacists' training needs with respect to oral SACT and their preferred methods of receiving education should be undertaken.

Limitations

The sample size was small, and data were collected retrospectively and relied on accurate dictation of clinic letters. There was no opportunity to speak to patients or prescribers. Episodes of unscheduled care in a hospital out with the study health

board could not be identified from the electronic patient record therefore full capture of this data cannot be confirmed. There was variability in the content of prescriber-dictated clinic letters and so some toxicity may not have been recorded. In addition, the patients may not have volunteered the information. The clinical pharmacist was not present at each of the patient's clinic appointments and relied on the pharmaceutical care plans and dictated letters to extract data. Any future work should be conducted prospectively at the point of prescribing. Further work will include a community pharmacist focus group and questionnaire to establish existing access to patient's clinical information, information needs of community pharmacists and levels of confidence in dealing with patients who are prescribed SACT.

Conclusion

The hypothesis that patients who received SACT for lung cancer experience toxicity which could be managed in primary care by community pharmacists was correct with caveats.

A selection of PCIs and SACT-associated toxicity could be managed by suitably trained and supported community pharmacists. Plans for sharing information and knowledge between care providers will help in the management of toxicities.

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Table 1: Study population patient characteristics

Patient characteristics, n = 50

Age (years) median (IQR)	66 (38, 82)		
Baseline weight (kg) median (IQR)	64.5 (39, 97)		
	NSCLC; n=29 (58%)	**SCLC**; n=20 (40%)	**Large cell**; n=1 (2%)
Gender, Female (27, 54%)	15	11	1
Smoker	16	12	
Non-smoker	10	4	1
Not recorded	3	4	
Performance status			
0	7	2	0
1	16	14	1
2	1	4	0
Not recorded	5	0	0
Baseline eGFR			
>60 ml/min	25	16	1
40-60 ml/min	4	4	0
Co-morbidities			
Cardiovascular	10	11	0
Respiratory	8	3	1
Endocrine	6	4	1
CNS	5	1	0
Musculoskeletal	4	3	0
Gastrointestinal	4	1	0
Cerebrovascular	2	1	0
Skin	2	0	0
Renal	1	1	0

Key
NSCLC: Non-small cell lung cancer; SCLC: Small cell lung cancer; eGFR: estimated glomerular filtration rate; CNS: central nervous system;

Table 2: SACT regimens prescribed for the study population

SACT for non-small cell lung cancer	**SACT for small cell lung cancer**	**SACT for large cell carcinoma**
Cisplatin & vinorelbine	Carboplatin & etoposide	Carboplatin & etoposide
Carboplatin & vinorelbine	Topotecan	
Carboplatin & pemetrexed	Carboplatin	
Carboplatin & gemcitabine	CAV (cyclophosphamide; doxorubicin; vincristine)	
Carboplatin & paclitaxel		
Carboplatin		
Erlotinib		

Table 3: Summary of SACT toxicity recorded in patient's medical records

Toxicity, any grade	**Reported episodes of toxicity, all regimens (n (%))**
Haematological	18 (21.6%)
Renal	18 (21.6%)
Fatigue	10 (12%)
Nausea & vomiting	9 (10.8%)
Constipation	5 (6%)
Diarrhoea	5 (6%)
Neurological	5 (6%)
Oral	3 (3.6%)
Infection	3 (3.6%)
Skin	3 (3.6%)
LFTs	2 (2.4%)
Decline in performance status	2 (2.4%)

Table 4: Number of recorded PCIs for parenteral, oral and combination SACT in the study population

Pharmaceutical care issue	Parenteral SACT	Oral SACT	Combination oral/parenteral SACT
Gastrointestinal: nausea and vomiting; mucositis; diarrhoea; constipation	CAV (n=1) Carboplatin & pemetrexed (n=1) Carboplatin & paclitaxel (n=1)	Erlotinib (n=3)	Cisplatin or carboplatin & vinorelbine (n=7) Carboplatin & etoposide (n=3)
Sepsis	Carboplatin & paclitaxel (n=1)		Carboplatin & etoposide (n=1)
Skin rash		Erlotinib (n=6)	
Renal/hepatic	Carboplatin & pemetrexed (n=3) Carboplatin & gemcitabine (n=1) CAV (n=1)	Erlotinib (n=1)	Cisplatin or carboplatin & vinorelbine (n=3) Carboplatin & etoposide (n=2)
Neurological			Cisplatin or carboplatin & vinorelbine (n=2) Carboplatin & etoposide (n=1)
Hypercalcaemia	Carboplatin & pemetrexed (n=2) CAV (n=1)		
Patient education	Carboplatin & pemetrexed (n=2) Carboplatin (n=1)	Erlotinib (n=4)	Cisplatin or carboplatin & vinorelbine (n=1)
Prescribing error/dose recalculation	Carboplatin (n=3) Carboplatin & pemetrexed (n=1)		Carboplatin & etoposide (n=2)
Drug interaction/non-formulary drug	Carboplatin & pemetrexed (n=1)	Erlotinb (n=2)	Carboplatin & etoposide (n= 1)
Pain			Carboplatin & etoposide (n=1)

Table 5: Number of PCIs by SACT regimen

Regimen	**Number of PCIs**	**Average number of PCIs per patient**
(with oral SACT)		
Carboplatin & etoposide (n=9)	11	1.2
Carboplatin & vinorelbine (n=1)	3	3.0
Cisplatin & vinorelbine (n=4)	10	2.5
Erlotinib (n=6)	16	2.6
Topotecan (n=1)	0	0
(parenteral only)		
CAV (n=4)	3	0.75
Carboplatin (n=8)	4	0.5
Carboplatin & gemcitabine (n=5)	1	0.2
Carboplatin & paclitaxel (n=1)	2	2.0
Carboplatin & pemetrexed (n=11)	10	0.9