Patients with Advanced Lung Cancer: Is there Scope to Discontinue Inappropriate Medication?

Abstract

Background

Polypharmacy – taking five or medications per day – is common in lung cancer patients. This patient group is prescribed medication to control acute symptoms associated with cancer and also to prevent or treat other long-term conditions. These medications increase the pill burden for the patient and also the probability of developing a drug-related toxicity.

Objective

To assess the prevalence of inappropriate medication in patients taking erlotinib for the treatment of advanced non-small cell lung cancer.

Method

This was a multicentre study across three sites in the North of England. Medication histories for patients receiving erlotinib were retrospectively extracted from medical notes and assessed by the clinical team (a consultant pharmacist, nurse specialist and clinical oncologist) to determine if the medication was appropriate or inappropriate. The clinical team considered the following factors when deciding if the medication was appropriate or inappropriate: remaining life expectancy of the patient, time until benefit of the treatment, goals of care and treatment targets.

Results

Among the 20 patients assessed, 19 (95 per cent) according to the clinical team were taking medications that were inappropriate. The mean number of medications the patients were taking was 8 (range 1 – 16) and the most common class of medication used were drugs affecting the Central Nervous System. In addition, there were 11 patients (55 per cent) who were taking erlotinib in combination with a proton pump inhibitor (PPI) – a clinically significant drug interaction that impairs the absorption of erlotinib.

Conclusions

Patients taking erlotinib for the treatment of advanced non-small cell lung cancer take many inappropriate medications for the treatment or prevention of long-term conditions. These patients should have their medications reviewed in the context of their original therapeutic goals.

Keywords: non-small cell lung cancer, erlotinib, limited life expectance, inappropriate medication

Impacts on Practice

- Clear guidelines are needed on discontinuing inappropriate medication in patients with advanced lung cancer;
- Wider information relating to patient medication history should be made available at the time of dispensing chemotherapy to facilitate a medication review; and,

- Oncology units should have a clear policy for pharmacy to actively screen the medication history of all patients with advanced non-small cell lung cancer to establish if they are taking any interacting medicines prior to initiating erlotinib.

Introduction

Polypharmacy is associated with an increased risk of developing a drug-related toxicity due to the potential of drug-drug and drug-disease interactions.[1,2] In cancer patients with limited life expectancy (LLE) – typically surviving for less than 1 year – polypharmacy is very common; medication is not only prescribed to control acute symptoms associated with cancer but is also used to prevent or treat other long-term conditions.[3] These patient groups also have unique and dynamic pharmacokinetic and pharmacodynamics parameters (e.g. variation in volume of distribution or altered drug excretion due to declining renal and / or hepatic function), which further increases the probability of developing a drug-related toxicity.[4,5]

In recent years, the problem of cancer patients with LLE developing a drug-related toxicity has been heightened by the introduction of targeted therapies – agents that block the growth and spread of cancer by interfering with specific cellular signals involved in tumor growth and progression. Indeed, while targeted therapies have significantly improved positive outcomes for patients, they have also increased the risk of developing a drug-related toxicity. For example, erlotinib – a tyrosine kinase inhibitor used for the treatment of advanced non-small cell lung cancer (NSCLC) – is metabolized, in part, by CYP1A1, CYP3A4 and CYP2D6, which significantly increases the risk of developing drug-drug interactions when using medicines that either inhibit or induce these isoenzymes – especially in patients with LLE.[6]

In view of the potential for polypharmacy to cause harm in cancer patients with LLE, it is therefore essential to review and optimise medication to align with therapeutic goals and life expectancy. This process may include discontinuing non-essential or inappropriate medication to reduce polypharmacy and, ultimately, the risk of developing a drug-related toxicity. To date, there is limited research that reports whether inappropriate medication is being discontinued in cancer patients with LLE taking a targeted therapy.

Aim of the Study

The objective of the study was to assess the prevalence of inappropriate medication in cancer patients taking erlotinib for the treatment of advanced non-small cell lung cancer.

Methods

This was a multicentre retrospective study across three oncology units in the North of England. All patients who had received erlotinib between April 2010 and April 2011 for the treatment of locally advanced or metastatic NSCLC after failure of previous chemotherapy were included in the study. Patients were excluded if the erlotinib was being used for another indication (e.g. for the treatment of metastatic pancreatic cancer).

Medication histories for patients who had received erlotinib in the study period were retrospectively extracted from medical notes and sorted according to categories in the British National Formulary (BNF). When there was an ambiguity around the indication of the prescribed medication (e.g. for a

medicine with several indications), the patient's GP was contacted by telephone to establish the original prescribing indication of the medicine. Once all of the medication was categorised, it was assessed by a consensus panel (a consultant pharmacist, nurse specialist and clinical oncologist) to determine if it was appropriate or inappropriate. The clinical team used a framework described by Holmes and colleagues[7] when deciding if the medication was appropriate or inappropriate; the following factors where considered: remaining life expectancy of the patient, time until benefit of the treatment, goals of care and treatment targets.

The study was certified for ethical approval in accordance with the University of Sunderland ethics committee by the senior researcher (AT).

Results

Twenty patients were included in the study; the mean number of medications taken was 8 (range 1 – 16) and the most common class of medication used were drugs affecting the Central Nervous System (Table 1). The distribution of medication among patients were as follows:

- 7 patients (35 per cent) were taking medications which affected the cardiovascular system, e.g. beta blocking drugs, lipid-lowering drugs;
- 13 patients (65 per cent) were taking drugs which affected the gastrointestinal system, e.g. anti-secretory drugs, mucosal protectants, anti-motility drugs and laxatives;
- 9 patients (45 per cent) were taking drugs which affected the respiritory system, e.g. bronchodilators, antihistamines and mucolytics; and,
- 6 patients (30 per cent) were taking drugs which affected the endocrine system, e.g. anti-diabetics, thyroid and anti-thyroid drugs and corticosteroids.

According to the consensus panel, 19 patients (95 per cent) were taking at least one inappropriate medication that could be discontinued; the mean number of medications per patient that were considered inappropriate was 3 (range 0 to 7).

The most commonly prescribed medication that was considered inappropriate were proton pump inhibiors (PPIs) in 11 patients (55 per cent); this medication was initiated in primary care by the patients' General Practitioner (GP) prior to erlotinib use. Other medication that was commonly prescribed in this patient group that was considered inappropriate were antiplatelets and lipid regulating drugs. Among the patients taking antiplatelets, 5 were talking aspirin, while 1 was using clopidogrel; both agents were used for secondary prevention of cardiovascular events. For patients taking lipid regulating agents, all 3 were taking HMG-CoA reductase inhibitors ("statins") for either primary or secondary prevention of cardiovascular events.

In contrast, the most common medication prescribed to this patient group that were considered appropriate were the corticosteroids and analgesics. Indeed, among the patients taking a corticosteroid, 6 were taking dexamethasone; this was initiated in secondary care and was either used as an appeptite supplement or to treat oedema associated with cerebral metastases. For patients using analgesics, 8 were taking NSAIDs, 9 opioids, and 10 non-opioids.

Discussion

Our results show that the majority of patients taking erlotinib with advanced lung cancer are using many inappropriate medications in view of their terminal prognosis. The futile use of medication in patients with LLE has been previously reported in the literature for patients with cancer, advanced dementia and several studies have also specifically examined statin use in patients with LLE. For example, Fede and colleagues assessed patients with advanced cancer and concluded among 87 patients, 21 were taking at least one unnecessary medication[8], while Stavrou and colleagues found that more than 30 per cent of patients who died of cancer were dispensed statins within 30 days of death.[9]

Patients undergoing treatment for terminal lung cancer can be frightened, upset or angry so the issue of discontinuing inappropriate medications is not a priority. However, once the patient has come to terms with their prognosis, a discussion regarding their medications should be instigated. The timing of this discussion is difficult and should be a shared decision between the patient and the healthcare team with careful explanation of why it is necessary to discontinue inappropriate medications. It is not clear who should instigate this discussion and recent work suggests that GPs would welcome training in shared care decision-making in relation to discontinuing inappropriate medication in elderly patients.[10] Interestingly, the same study showed that GPs perceive stopping preventative medication as being more difficult when compared with medication used to treat symptomatic conditions as they believe patients may interpret a proposal to stop preventive medication as a sign of having been given up on. Further work exploring the views of healthcare professionals regarding stopping inappropriate medication in a cancer context is warranted.

A key finding of this work also showed that more than half of our patient population were taking erlotinib in combination with a proton pump inhibitor (PPI). Given there is an established drug interaction between erlotinib and PPIs our results are of significant value. Indeed, the absorption of erlotinib is pH dependant and increasing the pH of the stomach significantly reduces the absorption of erlotinib; for example, omeprazole decreased the erlotinib exposure [AUC] and maximum concentration [Cmax] by 46 % and 61 %, respectively.[11.] Recent works suggests that using PPIs in combination with erlotinib does not appear to significantly reduce the efficacy of erlotinib.[16] However, given that this interaction has not been studied in a large scale clinical population, it would be prudent to avoid the combination of erlotinib and PPIs; if acid suppression is necessary a H_2 receptor antagonist, such as ranitidine, should be used with a staggered dosing regimen.[11]

There is the potential for pharmacists to become involved in the review of patients with terminal cancer to facilitate discontinuing inappropriate medication. Indeed, Conlon and colleagues have recently described a pharmacist-led intervention around psychotropic prescribing, which utilized recommendations from the STOPP-START and Beers criteria to minimize inappropriate medication use.[12] The STOPP-START[13] and Beers criteria[14] are both used for classifying appropriate and non-appropriate medications in the elderly and have clear limitations in palliative care.[15] However, these criteria used in combination with the framework developed by Holmes and colleagues[7] may prove to be a useful starting point for clinical pharmacists offering this service to patients with LLE.

While we believe these results are robust and have important implications for the treatment of lung cancer patients only patients from oncology units in the North of England were examined and the

sample size was relatively small. Generalisation of this work to all lung cancer patients in England and more widely should therefore be made carefully.

Conclusion

Patients taking erlotinib for the treatment of advanced or metastatic NSCLC take many inappropriate medications for the treatment or prevention of long-term conditions. These patients should have their medications reviewed in the context of their original therapeutic goals.

Conflicts of interest

None of the authors have any conflicts of interest concerning this work.

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Table 1. The type and frequency of medicine according to BNF classification

BNF Classification	Number of Medications
Cardiovascular system	
Beta-adrenoceptor blocking drugs	2
Drugs affecting RAS	3
Anti-platelets	6
Anticoagulants	3
Diuretics	3
Lipid regulating drugs	3
Nitrates	1
Calcium channel blockers	2
Total	**23**
GI system	
Anti-secretory drugs	11
Anti-diarrhoeals	1
Laxatives	8
Anti-spasmotics	1
Total	**21**
Respiratory system	
Bronchodilators	4
Corticosteroids	4
Anti-histamines	1
Mucolytics	2
Cough preparations	1
Total	**12**
Endocrine system	
Anti-diabetics	1
Thyroid and Anti-thyroid drugs	1
Corticosteroids	6
Drugs affecting bone metabolism	2
Total	**10**
CNS system	
Hypnotics and Anxiolytics	6
Psychoses and related disorders	1
Antiemetics	2
Antidepressants	3
Analgesics (NSAIDs)	8

Analgesics (Opioids)	9
Analgesics (Non-opioid)	12
Antiepileptics	5
Total	**46**
Miscellaneous	
Vitamins, minerals and herbal supplements	38
Total	**38**