Cancer is more common in older than younger Australians. In 2009, 73.5% of new cancer cases diagnosed in men were in those aged 60 years and over, and 63.6% in women of the same age group. Many older people are medically fit before being diagnosed with cancer; however others have chronic medical conditions such as hypertension, cardiovascular disease, diabetes, osteoarthritis etc. These comorbid conditions can impact on prognosis and treatment tolerability in people diagnosed with cancer. An additional consideration is the medications, prescribed by their general practitioner (GP) or other specialists, which they are already taking. Cancer patients may also use over the counter medicines and complementary and alternative medicines (CAM), including herbal or other supplements which they may or may not mention to their doctor. Starting cancer chemotherapy with combination intravenous cytotoxic drugs, or oral ‘targeted’ agents, and additional supportive medications to prevent side-effects or manage symptoms, can lead to patients taking multiple medications, which is referred to as polypharmacy.

There are a number of definitions for ‘polypharmacy’. One numerical definition is a patient taking five or more different medications, although others set this number at four or six medications. It is notable that this definition does not take into account ‘pill burden’ or number of different doses being taken each day. Others define polypharmacy more broadly as occurring when a patient is taking more drugs than are clinically indicated, taking unintended therapeutically duplicate medications, or taking potentially inappropriate medicines. Perhaps more important than having an exact definition is to understand what effect polypharmacy might have on an individual cancer patient.

Incidence of polypharmacy in cancer patients

Attention has recently turned towards polypharmacy issues in older cancer patients with the publication of several studies. The first 200 newly diagnosed cancer patients aged 70 years assessed at an Australian geriatric oncology clinic were taking a mean of five medications (range 0 to 18) before they started chemotherapy.

A cross-sectional study of 117 patients aged >65 years in US outpatient oncology clinics took 7.3 ±3.4 medications, comprising 5.6 ±3.1 prescribed medications, and 1.7±1.6 non-prescribed medications. In this study, the prevalence of polypharmacy and potentially inappropriate medicines use was 80% and 41% respectively, with the odds of using potentially inappropriate medicines increasing by 18% for each increase in additional medication. These results indicate that polypharmacy in cancer patients is an issue of concern that needs to be considered and managed by the treating team.

Problems associated with polypharmacy

Polypharmacy and use of potentially inappropriate medicines in older people increase the incidence of adverse drug reactions, which is defined as ‘the unintended noxious response to one or more drugs’. More than half of a sample of 100 patient with metastasis cancer taking medication for comorbid disease reported side-effects, including dizziness and postural hypotension, muscular aches, bruising, indigestion and/or reflux. In frail elderly patients, functionality is frequently affected by adverse drug effects which commonly include anticholinergic symptoms, changes in mental status, mood and behaviour and GI tract disturbances (constipation or diarrhoea). Undesirable health outcomes of polypharmacy have included confusion, poor adherence, delirium, impaired balance leading to falls, fractures, adverse drug reaction related hospitalisation, nursing home placement and even death. In older cancer populations, polypharmacy may be associated with general functional decline, but also geriatric syndromes such as urinary incontinence, cognitive impairment or falls.

Management of polypharmacy in older cancer patients

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Abstract

Many older people newly diagnosed with cancer are taking medications for comorbid conditions, or as primary or secondary disease prophylaxis. The commencement of chemotherapy and the introduction of associated medications to treat symptoms or prevent toxicity necessitate identification and management of polypharmacy. Polypharmacy refers to the use of multiple medications. This article describes a four step approach to manage polypharmacy in the ambulatory cancer care setting. Step 1 - identifying all of the medications a patient is taking including prescribed, self-prescribed, over the counter and/or complementary medicines. Step 2 - checking for potentially inappropriate medications. Step 3 - checking for drug interactions. Step 4 - considering de-prescribing. A multi-disciplinary team approach is key to managing polypharmacy in older cancer patients.
There is rising clinical concern about the potential for drug-drug interactions as polypharmacy increases, which is amplified in older cancer patients who may already have age-related changes in drug pharmacokinetics, such as altered absorption, and renal and hepatic dysfunction. 2,3,5,10 The outcomes of drug-drug interactions can range from theoretical changes in the bioavailability of one or both drugs, with no clinical significance or requirement to change dose or drug, to hospital admission and potentially life threatening events. 2,10 For example, a retrospective review identified 21 cancer patients started on oral capecitabine who were already taking the coumarin anticoagulant, warfarin. 11 Bleeding requiring hospital admission and/or transfusion occurred in four of the patients. 11 Warfarin is frequently used for primary or secondary stroke prevention in older people, as well as for clotting disorders that are not uncommonly associated with cancer. This interaction is likely due to inhibition of cytochrome P450 (CYP450) 2C9 by capecitabine and/or its metabolites. 12 Patients taking warfarin who start capecitabine should be monitored regularly for alterations in their coagulation parameters and warfarin dose adjusted as required. 12 Recently, interest has focused on the escalating use of oral ‘targeted’ agents for treating a number of cancers and the potential impact on drug interactions in this population. A retrospective review of nine targeted agents (dasatinib, erlotinib, everolimus, imatinib, lapatinib, nilotinib, pazopanib, sorafenib and sunitinib), all of which are commonly used in Australia, found that the incidence of co-prescribing of potentially interacting drugs was high. 13 While this study identified the number of patients exposed to potential drug interactions, it was not designed to determine how many, if any, patients actually experienced a clinically significant interaction. 13 However, the results certainly raised concern, and illustrate the importance of clinicians being vigilant for interacting drugs when prescribing oral cancer therapy. Drug-drug interactions are not limited to prescribed medications. Use of certain over-the-counter and CAM has led to serious interactions with chemotherapy. 2,14,15 Cancer patients in general, but also older cancer patients, have been found to take a range of different CAM, including agents which have multiple effects on the CYP450-mediated and P-glycoprotein-mediated metabolic pathways, such as garlic and ginkgo. 14,15 St John’s wort, also a CYP450 3A inducer, may be self-prescribed by patients, including those with cancer, for depression. 2,15 If it is taken with irinotecan or imatinib, St John’s wort can reduce the anti-cancer effect of both drugs, with the potential to adversely influence treatment outcome. 2,15 Patient adherence to a prescribed treatment is affected by the number of medications a person is taking, as well as the complexity of the regimen. 5,6,7 Increased healthcare costs include cost of supply of inappropriate or duplicate medications, additional patient monitoring that may be required and emergency department visits or hospitalisation due to serious adverse events, or as a result of unexpected drug interactions. 2

Tackling polypharmacy
There are many interventions that have been aimed at improving appropriate polypharmacy including educational program for prescribers, organisational interventions such as pharmacist led medication review services or specialist clinics, clinical decision support systems, and risk screening tools. 9 For the purposes of this article, a stepwise care pathway is suggested (figure 1).

Figure 1: Polypharmacy care pathway

Step 1: Identify all of the medications a patient is taking
The need for effective communication between all of a patient’s healthcare providers, including his or her GP, is essential to accurately determine a patient’s medications and document in his or her cancer care medical record. To ensure the treating team are fully aware of all medications that a newly referred cancer patient is taking before chemotherapy or supportive medication is prescribed, a comprehensive medication history is essential. 2 A medication list generated by the patient’s GP is a useful starting point, however clinicians need to be mindful that these lists may not reflect actual medication usage, recent verbal drug or dose changes, and are very unlikely to list all of the patient’s over the counter or CAMs. While most patients admitted to public hospitals in Australia have a medication history conducted by a pharmacist within a set time of hospital admission, this may not be the case in ambulatory clinics where cancer patients are most commonly treated. They deserve the same attention from the pharmacist, which might require communication with the patient’s community pharmacy or GP. Some cancer centres have a comprehensive medication history interview with a pharmacist built into pre-chemotherapy appointments, but this is not always the norm. The medication history can be facilitated by the use of the so-called ‘brown bag’ technique, where the patient brings all of their medicines with them for review. 2 Other methods that have been found useful in the literature, include providing patients with checklists of common prescription and/or non-prescription drugs, vitamins and supplements that they can complete before their initial cancer assessment and planning interview. 2,15
Electronic medical records used in some clinics in a US study were found to be significantly more complete for prescribed medicines (83%) than those using paper records (69%). However, the percentage of recorded non-prescription medicines and other preparations patients were taking was very low. Currently in Australia, and many other countries, there is no connection between dispensing databases kept in community pharmacies, where most patients’ medicines are dispensed, and those used by the hospital pharmacy, chemotherapy infusion centre or the oncology electronic chemotherapy prescribing system used by the oncologist/haematologist (where that is in place). It remains to be seen how the linkage of data between various systems progresses in future.

**Step 2: Checking for potentially inappropriate medications**

The National Comprehensive Cancer Network Senior Adult Oncology Guidelines recommend that medication review for duplication and appropriate use should be performed at every visit. Several tools for identifying potentially inappropriate medicines in older patients have been described. The well-known Beers criteria were developed in the US in 1991 and have been most recently revised by the American Geriatrics Society. This list of inappropriate medications includes drugs with a long half-life, with side-effects such as sedation or anticholinergic effects, known high risk medications when safer alternatives exist, ineffective drugs, doses of drugs that should not be exceeded, and drug–disease and drug–drug interactions that should be avoided. The drug classes (table 1) that could be targeted for discontinuation in collaboration with the patient’s primary care provider include tricyclic antidepressants, sedating antihistamines, long acting benzodiazepines associated with increased sedation, analgesics containing dextropropoxyphene or tramadol, and some non-steroidal anti-inflammatory drugs such as indomethacin. However, the applicability of this de-prescribing regimen to Australian cancer patients has not been determined at this stage, especially as many of the drugs listed are not currently used in this country.

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Reason for considering discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic antidepressants</td>
<td>Strong anticholinergic and sedating properties.</td>
</tr>
<tr>
<td>Long acting benzodiazepines</td>
<td>Long T1/2 in elderly (often several days) - prolonged sedation and increased risk of falls and fractures.</td>
</tr>
<tr>
<td>Sedating antihistamines</td>
<td>Increased risk of falls and fractures.</td>
</tr>
<tr>
<td>Analgesics containing dextropropoxyphene</td>
<td>No added benefit but added CNS side-effects and increased risk of falls and fractures.</td>
</tr>
<tr>
<td>Some NSAIDs including indomethacin</td>
<td>Highest incidence of CNS effects.</td>
</tr>
</tbody>
</table>

NSAIDs = non-steroidal anti-inflammatory drugs; T ½ = half life; CNS = central nervous system

Other tools that may be helpful include the Medication Appropriateness Index, and the STOPP (The Screening Tool of Older Persons’ Potentially Inappropriate Prescriptions) tool. STOPP was developed in Ireland by a multidisciplinary team including geriatricians, primary care physicians, pharmacists and others. Although not yet applied to the older cancer patient setting, STOPP includes 65 indicators mostly relating to drug-drug and drug-disease interactions that highlight falls risk. In the cancer setting, a group of oncologists developed their own classification of unnecessary medications based on whether or not there was a clear medical indication for continuing use to treat co-morbid conditions in patients with advanced cancer, some of whom were on chemotherapy. The potentially unnecessary medications included statins, anti-hypertensives, anti-diabetics and gastric protectants. This six month prospective study found 21 patients (24%, 95% CI 15.6-34.5%) were taking at least one unnecessary medication, with the most common being gastric protective agents for which there was no clear indication in 11 patients. A Prescribing Indicators Tool was developed specifically for elderly Australians, however not those with cancer. The tool has 48 indicators, including: 18 which concern avoidance of medications in a specific disease; 19 for recommended treatment; four indicate monitoring is required; three concern specific drug interactions; and the last four are single indicators - drug interactions, drug changes in past 90 days, smoking and vaccination status. The feasibility of using the prescribing indicators tool with older cancer patients and its effectiveness is yet to be demonstrated.

The National Comprehensive Cancer Network guidelines more simply advise special considerations for over or underuse, duration of therapy and dosage when using the following classes of medications: benzodiazepines, anticholinergics; antipsychotics; opioids and corticosteroids, all of which may well be required in older cancer patients. While tools for determining inappropriate medications now exist, their application in older cancer patients is far from standard practice.

**Step 3: Checking for drug interactions**

There are numerous resources that can be used by busy clinicians to check for drug interactions, ranging from standard textbooks which vary in frequency of updating, to point-of-care online resources, including some specifically for checking CAM interactions. Interaction checkers are also built in to many electronic prescribing or dispensing systems, but they are of varying accuracy. If they are not providing clinically significant information and importantly, useful management advice, the information provided by these checkers can lead to ‘alert fatigue’. The tiering of alerts to show only those with the potential for serious outcomes is one possible solution to address this. Not all drug-drug interactions require therapy changes, but clinicians need to be aware of any potential problems to allow additional monitoring to be implemented.

Checking chemotherapy prescriptions for potential drug-drug interactions with the patient’s concomitant medications is one of the standard components of medication therapy management in cancer patients. In a prospective study involving pharmacists in a cancer
centre in Singapore, a process was adopted that included: a comprehensive medication review to identify, resolve and prevent medication-related problems; formulating a medication treatment plan; selecting, initiating, modifying, or administering medication therapy; providing verbal education to enhance patient adherence; and communicating essential information to the patient’s other primary care providers. Drug interactions were the most common drug related problem seen in about 30% of patients. This study supports the team approach to managing older cancer patients.

**Step 4: De-prescribing**

Medications identified by the methods described above as being unnecessary, inappropriate, or potentially harmful can be considered for discontinuation or so called ‘de-prescribing’. While this may take place on an informal basis between oncologists and their older cancer patients in Australia, there do not appear to be any specifically cancer-related publications to assist the oncologist or the cancer team with this process. Taking established methods from the geriatric patient setting, such steps will most likely include assessing the patient including their frailty and life expectancy, determining and discussing goals with the patient and/or carer and then reviewing, assessing and optimising medications, as outlined in step 2 above. At this stage, the discussion about ceasing unneeded medications can begin in a structured way, in collaboration with the patient, their family or carer as appropriate, and GP.

**Conclusions**

Polypharmacy is a growing concern for clinicians involved in managing older cancer patients. Not all of the medications an older cancer patient is taking need to be ceased before starting chemotherapy, as many are appropriately prescribed to manage their co-morbid conditions. However, it is important that the treating team is aware of every medication the patient is taking to ensure safe application of the selected chemotherapy without harm resulting from adverse effects or drug interactions. Ideally, a medication therapy management service should be available to all our older cancer patients to facilitate the process. The systematic application of the four step approach is recommended for adoption by multidisciplinary cancer care teams to minimise the adverse effects of polypharmacy in older cancer patients.

**References**