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Polypharmacy and the management of the older cancer patient

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Aging is associated with polymorbidity and polypharmacy. In the absence of a consensual definition, polypharmacy has been defined according to the number of drugs that an individual takes or to the presence of the risk of at least one severe drug interaction. In older cancer patients, polypharmacy is at least as common as it is in individuals of the same age without cancer. The management of cancer itself may result in the addition of more medications to counteract the adverse effects of antineoplastic treatment. Polypharmacy may be necessary to control the multiple health conditions of the older person, but it may represent a risk factor for more complications from antineoplastic therapy, and it may affect the outcome of cancer treatment. Polypharmacy is also associated with increased cost. The criteria proposed for the management of polypharmacy include the assessment that all medical conditions are properly treated, the avoidance of drug interactions, and of drugs that may compromise the outcome of antineoplastic treatment and the choice of drugs with the lowest risk of complications in older individuals.

introduction

The intake of multiple medications is a common event in the management of older individuals. Increased polypharmacy is associated with age because the prevalence of polymorbidity increases with age [1–6]. Other contributing factors may include: the absence of a primary care provider able to coordinate the care of different specialists [7] and increased use of alternative forms of treatments [8]. In addition, older individuals may be more likely to persist in taking medications that are no longer needed, due in large part to misunderstanding and miscommunication when care is coordinated across multiple clinicians and patients transfer between multiple sites of care [9].

The use of multiple medications may lead to the addition of still more drugs to the medication regimen, as new medications are prescribed to counteract the complications of previous medications. This is particularly true for the management of cancer with cytotoxic chemotherapy. Prevention and mitigation of chemotherapy-induced nausea and vomiting, which is almost universal, often requires the administration of serotonin uptake inhibitors that can cause constipation and headaches, and of glucocorticoids that may cause hyperglycemia, gastric distress, and insomnia [10]. Supportive care itself is a cause of complications. Hemopoietic growth factors may cause bone pain [11] and erythropoietin deep vein thrombosis [12].

In situations such as these, the use of medications to counteract the adverse effects of essential drugs may be necessary and unavoidable. In other cases, the ‘prescribing

cascade’ of using one drug to treat adverse effects of another drug can be counterproductive and inappropriate [13]. This often occurs when adverse effects caused by one drug are misattributed to an underlying disease rather than being properly recognized as an adverse drug reaction. For example, a patient taking a dihydropyridine calcium-channel blocker who develops lower extremity edema may be thought to have new-onset heart failure or venous insufficiency and treated with furosemide, rather than properly diagnosing the condition as an adverse drug reaction and withdrawing the offending therapy. Subsequent development of incontinence may lead to prescribing of a bladder antimuscarinic agent, which in turn leads to worsening cognition, which in turn may lead to prescribing of a cholinesterase inhibitor; and so forth.

Polypharmacy itself is not intrinsically good or bad. The use of multiple medications increases the risk of side-effects, drug–drug interactions, and increased treatment cost. At the same time, the medications used in polypharmacy may prolong the survival and the functional independence of older individuals. For example filgrastim and pegfilgrastim allow the cure of older patients with large-cell lymphoma and prevent the risk of mortality, hospitalization, and deconditioning, despite causing bone pain [14]. The correction of anemia with erythropoietin reduces the need of blood transfusion and the risk of deconditioning from fatigue [15].

As a result, optimal management of polypharmacy cannot be a one-size-fits-all approach, but rather is based on a careful and complex assessment of potential benefits and risks [9]. For this reason, it is important to establish a management frame of reference that may be applied to an evolving situation. The goal of this article is to study the management of polypharmacy in older cancer patients after reviewing the prevalence and clinical consequences of this condition. In concluding, we will propose a

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research agenda for an ongoing assessment of polypharmacy in a medical system that is rapidly changing.

cancer, age, and prevalence of polypharmacy

The definition of polypharmacy is controversial and includes the number of drugs that a patient receives, the presence of one or more inappropriate medications, or a combination of both [16]. The appropriateness of a medication can in part be established according to criteria for older adults that identify drugs that confer high risk of adverse effects relative to their benefits, or which pose a substantial risk of dangerous drug–drug or drug–disease interactions. Of these, the Beers Criteria are the best known [17]. Drug appropriateness may also be rated according to the Medication Appropriateness Index (MAI) [16]. The MAI provides a systematic method for reviewing ten elements of medication appropriateness, including indications, effectiveness, dosage, duration of therapy, drug–drug interactions, drug–disease interactions, therapeutic duplication, and directions.

While polypharmacy is known to be common in the general population of older adults, information related to polypharmacy in older cancer patients is limited. In 2001, the National Cancer Institute and the National Institute of Aging held a combined workshop on cancer in the elderly [18], but the issue of polypharmacy received little attention.

Perhaps the most informative study was conducted in Denmark, where a National Health care system allowed matching of patients in a nationwide cancer registry with the record of the medications prescribed to each patient. Jorgensen et al. [19] reported drug use by elderly Danish cancer patients between 1996 and 2006. They found that 35% of cancer patients 70 and older were taking five or more drugs at the time of diagnosis and this number increased with the age (39% for octogenarians and 41% for nonagenarians). Polypharmacy was more prevalent among older than younger cancer patients, and was more prevalent among older cancer patients with cancer than age-matched controls without cancer. Interestingly, the increase in number of prescription drugs started occurring 6 months prior the diagnosis of cancer, seemingly as the consequence of early cancer symptoms.

Other studies have also evaluated polypharmacy in ambulatory patients with cancer. In a pilot study, newly diagnosed cancer patients aged 65 and older in Quebec were taking an average of five medications at the time of diagnosis [20]. Not unexpectedly, the number of medications increased with the progression of the

disease, but for unexplained reasons, the risk of drug interactions was higher among patients not receiving systemic anticancer treatment. Among 117 newly diagnosed cancer patients age 65 and older, at an academic medical center in Cleveland, USA, 80% of patients were taking five or more medications, and 41% were taking one or more drugs considered potentially inappropriate by the Beers criteria [21]. Drug–drug interactions are also common among older cancer patients. Among 405 cancer patients receiving systemic chemotherapy at the Princess Margaret Hospital Oncology Clinic in Toronto, 27% had at least one potential drug–drug interaction, the strong majority of which were of major or moderate severity [22]. In addition, 8% of these patients were taking duplicate medications. In the same institution, drug interactions were present in 31% of patients with cancer who were receiving palliative care, and increased with the age of the patients [23].

Other studies have been carried out in hospitalized cancer patients. In 47 patients aged 65 and older admitted to a newly instituted Oncology-Acute care for the Elders unit in St Louis, USA, 21% were receiving one or more potentially inappropriate medications at the time of admission [24].

From this limited information, one may conclude that older cancer patients have a risk of polypharmacy as high as, and maybe higher than patients of the same age without cancer and that age is a risk factor for polypharmacy among cancer patients.

risks and complications of polypharmacy

The risks of polypharmacy are well defined (Table 1) [9, 25]. It is well established that the risk of adverse drug reactions increases with the number of drugs, and in fact, polypharmacy is the single strongest risk factor for adverse drug reactions [9, 26].

Likewise, the risk of drug–drug interactions increases with the number of drugs taken. In a study of 282 cancer patients at our institution [27], there were 851 potential drug interactions (PDI), with 75% of patients having at least one PDI. Overall, 95 PDIs had the highest level of clinical significance ('level 1' PDIs), 225 involved chemotherapy drugs, and 5 involved vitamins, supplements, or herbals. The risk of severe chemotherapy-related adverse events was associated with total number of PDIs [odds ratio (OR) = 1.17, 95% confidence interval (CI) 1.01–1.35], number of level 1 PDIs (OR = 1.94, 95% CI 1.21–3.10), and number of level 1 PDIs involving chemotherapeutics (OR = 3.01, 95% CI 1.30–6.97). This study demonstrated that PDIs may underlie a substantial number of chemotherapy-related complications, even when they do not involve cytotoxic or targeted agents. These findings were confirmed in another study which demonstrated that polypharmacy was associated with increased risk of irinotecan-related complications even when there were no clear drug interactions with irinotecan [28]. In addition to causing increased risk of adverse events, drug–drug interactions may also compromise the effectiveness of antineoplastic agents. For example, most of the activity of the Selective Estrogen Receptor Modulator Tamoxifen may depend upon its transformation to hydroxy-tamoxifen by the P450 microsomal system in the liver [29]. Medications that inhibit this system may interfere with the activity of tamoxifen. It should also be emphasized that

Table 1. Medication-related problems associated with polypharmacy

Adverse drug reactions
Duplication of therapy
Adverse drug–drug interactions
Adverse drug–disease interactions
Adherence to treatment
Cost

medications may have varying effects on tumor growth, both by potentiating the effectiveness of antineoplastic agents and through other mechanisms. For example, calcium channel blockers in high doses may reverse multidrug resistance of tumor cells [30], and insulin may stimulate [31] while metformin may inhibit [32] tumor growth.

Another implication of polypharmacy is its effect on medication adherence. Medication adherence may be adversely affected by use of multiple drugs [9, 16, 25], although it is important to note that the total number of medications may be less important than the frequency of dosing [33, 34]. For example it may be easier and more acceptable for patients to take 10 medications once per day than to take five medications that require dosing three or four times per day. In older individuals, adherence may also be impaired by other factors including memory disorders and limited resources. Failure to take the medications properly may reduce the effectiveness of antineoplastic drugs and compromise the outcome of cancer treatment.

Finally, the cost of a patient's treatment often increases with the number of drugs that are prescribed. Financial toxic effect may have both personal and societal consequences. At a personal level, it may impede patients' ability to take medications needed to treat their cancer and other conditions, or cause patients to spend so much money on their medications that insufficient funds remain to purchase food, housing, transportation, and other essential needs. At a societal level, it may drain common resources and prevent a number of important health-related projects.

management of polypharmacy

The goals of medication management of older cancer patients include reduction of adverse drug reactions, elimination of redundancy and duplication, prevention of negative impact of drugs on cancer and its treatment, improved adherence of patients to antineoplastic treatment, and overall reduction of management cost.

The effectiveness of medication management in cancer patients with polypharmacy has not been well studied. In the general geriatric population, a number of randomized, controlled studies have been conducted and are summarized in a recent review [9]. These studies included interventions that employed different strategies. In some studies, a pharmacist reviewed the patient's medications and recommended appropriate changes to the patient's usual physician [35–37]; settings of these studies included an outpatient VA clinic [35], a combination of six private practices [36], and home visit by a pharmacist [37]. In other studies, conducted in an outpatient geriatric clinic [38] and at 11 outpatient Veterans Hospital clinics [26], medications were reviewed by a multidisciplinary team and the final recommendations were conveyed to the treating physician. In another study, conducted in 18 rural clinics in the United States, the electronic medical record of the patient was reviewed by a geriatric pharmacist or a geriatrician, and an electronic recommendation was sent to the treating physician about modifying treatment with psychoactive agents [39].

In four of seven studies, the intervention resulted in a reduction in the number of medications prescribed [35–38]. No

study demonstrated an improvement in adverse drug reactions, health-related quality of life, or hospital admissions, although these studies were underpowered to detect clinically important differences in these important events. Of note, the largest study did find a reduction in rates of severe adverse drug events (ADEs), but not ADEs overall [26].

While medication management interventions seem generally effective at reducing the number of medications used, the limited power of these studies makes it difficult to draw firm conclusions about whether or not these interventions are effective at reducing major adverse clinical events. Other limitations in interpretation related to all studies include the diversity of the patients, the duration of the intervention, and the potential spillover effects to the control groups. To resolve these uncertainties, studies are needed in older cancer patients to establish whether optimal medication management results in decreased risk of complications from antineoplastic treatment and improved tumor response to the treatment, in addition to a reduction of drug adverse events and cost.

In the absence of more data, a reasonable approach to older cancer patients with polypharmacy includes a periodic reconciliation of medications [40]. This includes not only ensuring that medication lists are clearly understood and consistent between the patient and his or her physician(s), but also ensuring that the medication regimen is best suited to the circumstances of that patient. The following questions can be useful:

- Is there a proper indication for each medication?
- Is the medication achieving the desired effect (e.g. for a pain medication, is the pain controlled?)
- Does the patient present with nonspecific symptoms (for example fatigue, impaired cognition) that may be ascribed to some of the medications?
- Are the medications prescribed at an appropriate dose?
- Is there potential for clinically important drug–drug interactions?
- May some of the drugs interfere with the antineoplastic treatment?
- What is the risk of drug–tumor interactions?
- Does the patient adhere to the treatment plan?
- Are there conditions that need treatment and at present are left untreated?

As metastatic cancer is a life-limiting disease, the life expectancy of the patient may represent an indication whether to pursue some goals which may not yield benefits for several years after treatment begins. These include tight control of blood pressure, hyperglycemia, and serum cholesterol.

The optimal timing for a medication review is unknown, but is useful to consider at least once per year. In addition, at each clinic visit, it is reasonable to check whether the patient is taking new medications and what is the potential health effect of these new drugs.

Ideally, the older cancer patients should be managed by an interdisciplinary team that includes a clinical pharmacist [41, 42], who often is the best qualified person for medication review. Clearly, all members of the team should be involved in reporting conditions that may be related to polypharmacy and

the occurrence of new prescriptions. Even in the absence of the interdisciplinary team, the medication review is often best accomplished by a clinical pharmacist working with the oncology team.

perspectives on polypharmacy and geriatric oncology

Medicine is rapidly evolving and the evaluation and the management of polypharmacy should be considered a moving target. In a nondistant future, medication management in older patients with cancer will be affected by the development of genomics and proteomics. These emerging techniques will allow targeting of antineoplastic treatments based on the patient's pharmacogenomic profile, which may help predict the pharmacokinetics, effectiveness, and risk of adverse effects of drugs for that particular patient.

In the case of older cancer patients, a number of specific questions need to be addressed including:

- Are polypharmacy and/or specific medications an independent risk factor for complications of cytotoxic chemotherapy? Two models that predict the risk of chemo toxic effect in older cancer patients have been developed and validated based on the type of chemotherapy and on the comprehensive Geriatric assessment [43, 44]. These models may represent a matrix in which to insert the effects of polypharmacy and specific non-oncology medications.
- Does polypharmacy and/or specific medications affect the effectiveness of antineoplastic treatment?
- Does polypharmacy and/or specific medications affect tumor growth?
- Which medication management interventions are effective in improving outcomes of care in older patients with cancer?

conclusions

Polypharmacy is common among older cancer patients and is associated with a number of unfavorable effects, including increased risk of chemotherapy related toxic effect. Limited data from clinical trials make it difficult to conclude which methods are best for improving medication use and outcomes in older adults with cancer. However, periodic drug reconciliation, optimally conducted with the help of a multidisciplinary team including a pharmacist, appears helpful and advisable to prevent adverse drug reactions and unfavorable drug interactions.

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disclosure

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