Prescribing for Older Patients With Cancer

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Abstract: Pharmacotherapy in the elderly is very complex owing to age-related physiologic changes, the presence of multiple comorbidities, the use of multiple medications, the involvement of multiple prescribers and pharmacies, and an increased prevalence of cognitive deficits. The treatment of cancer and the management of symptoms related to therapy-induced toxicity significantly add to this complexity, with an increased risk of drug interactions, using potentially inappropriate medications (PIMs), and adverse drug reactions. There are several ways to evaluate inappropriate prescribing, with various levels of support for their use. We review the most widely used. Older adults are more susceptible than younger ones to chemotherapy toxicity, and may require dose modifications. Before starting therapy, the goals of care should be clearly defined and the general state of the patient should be assessed using some form of geriatric evaluation. Changes in the pharmacokinetics of the drugs related to aging and the possibility of end-organ dysfunction must be taken into consideration, particularly the age-related decline of glomerular filtration rate that is not always reflected by an increase in serum creatinine. The treatment plan for the older adult needs to be carefully defined in order to prevent adverse events, and allow the patient to benefit from treatment without a major impact on quality of life.

Introduction

Prescribing for older patients is extremely challenging. Men and women 65 years of age or older are the biggest consumers of medications.[1] Nearly one-third of community-dwelling adults age 65 or older take more than 5 prescription medications, and almost 20% take 10 or more. Among older adults, 42% take at least 1 over-the-counter drug and 49% take at least 1 nutritional supplement.[1,2] Pharmacotherapy of the elderly is very complex because of age-related physiologic changes, the presence of multiple comorbidities, and the use of multiple medications, prescribers, and pharmacies. In addition, patients' cognitive impairments and functional difficulties,

as well as caregiver issues, play a large role in errors and lack of adherence.[3]

Patients with cancer usually take multiple medications, not only for the treatment of the cancer and other comorbidities but also for supportive care and the management of symptoms related to therapy-induced toxicity.[4] The prevalence rates of polypharmacy and potentially inappropriate medications (PIMs) in older adults with newly diagnosed cancer were 80% and 41%, respectively, in 1 study. These factors, in turn, led to increases in adverse drug events (ADEs) and morbidity.[5] Polypharmacy and nonadherence are well-documented problems among elderly patients.[6] With the development of oral anticancer drugs, adherence has become an important factor in the success of treatment.[7]

This review describes the age-related changes that influence the prescribing of medication for older patients with cancer, the incidence of polypharmacy in this population, and the consequences of polypharmacy. It describes the most useful tools for the evaluation of PIMs, and reviews the literature examining the prescribing of chemotherapy in the elderly.

Pharmacotherapy in Older Patients

Successful pharmacotherapy requires the correct drug at the correct dose for the correct patient. Achieving this goal is difficult in older adults. Age-related physiologic changes and disease-related changes in organ function affect the body's handling of drugs (pharmacokinetics) and its response to drugs (pharmacodynamics). These changes have been well described and are summarized in Table 1.[3,8-10]

Table 1. Age-Related Factors Potentially Influencing Pharmacokinetics

Absorption
Controllable
Concomitant medications
Adherence
Not controllable
Reduced gastric secretion, gastric emptying, and gastrointestinal motility
Diminished splanchnic blood flow
Decreased absorption surface
Distribution
Changes in body composition
Doubling of fat content
Decrease in intracellular water
Reduction in albumin concentration (etoposide, taxanes highly protein-bound)
Anemia
Increase in volume of distribution
Lower peak concentration and prolonged terminal half-life
Metabolism
Reduced liver flow
Decreased liver size
Possible related changes in cytochrome P450 microsomal systems
Cytochrome P450 inhibitors (eg, grapefruit juice)
Cytochrome P450 inducers (eg, phenobarbital)
Drug interactions leading to adverse events
Excretion
Decline in glomerular filtrate rate
Additional effects of comorbid conditions on renal function

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Pharmacokinetics

Pharmacokinetics defines the time course of a drug and its metabolites throughout the body with respect to 4 parameters: absorption, distribution, metabolism, and excretion. Absorption undergoes the fewest changes with aging. Drug-drug, drug-disease, and drug-food interactions are the most likely sources of altered absorption. Drug distribution is altered by age-associated changes in body composition. With the decrease in lean body mass and increase in body fat as we get older, hydrophilic drugs have a lower volume of distribution, and lower doses result in higher drug concentrations. Conversely, lipophilic drugs have an increased volume of distribution; they take longer to reach a steady state and longer to be excreted.[8] The liver is the most common site of drug metabolism. Aging is associated with a decreased clearance of drugs metabolized by the liver through the type 1 pathway of reactions—that is, oxidative or reduction reactions catalyzed by the enzymes of the cytochrome P450 (CYP) system. Drug interactions involving the CYP system and their clinical consequences are more common in the elderly, resulting from either the induction or inhibition of enzymes by a variety of prescription drugs (eg, tricyclic antidepressants, selective serotonin reuptake inhibitors, paclitaxel, docetaxel), over-the-counter supplements, foods, chemicals, or toxins. It is particularly important to check for drug interactions at the CYP system level before starting a patient on any new medication, especially a chemotherapeutic agent. Elimination refers to a drug's final route of exit from the body. For most drugs, elimination involves the kidneys. Renal function begins to decline when people reach their mid-40s and continues to decline by an average of 10% per decade. Although some of the observed decline is likely due to changes in the vasculature, much of it is associated with the development of age-associated glomerulosclerosis.[11] The serum creatinine concentration in the elderly patient is a poor estimator of renal function. Guidelines have been published regarding appropriate dose adjustment.[12]

Pharmacodynamics

Pharmacodynamic changes have been more difficult to define than pharmacokinetic changes because the effect of many drugs is magnified in the elderly by reduced drug clearance, which results in an increased serum concentration. However, there are well-documented age-related changes in pharmacodynamics with significant clinical consequences. It has been generally acknowledged that the elderly are more susceptible to certain drug effects, often resulting in increased toxicity. Examples include increased cardiac toxicity from anthracyclines[13] and increased neurotoxicity.[14] The benzodiazepines are another example. Older adults exhibit more sedation and a lower level of performance than younger persons do at the same plasma concentration.[15] Loss of neuronal substance, decreased synaptic activity, impaired glucose metabolism in the brain, and the fact that drugs penetrate the central nervous system more readily are responsible for the greater susceptibility and exaggerated response of older persons to drugs that interact with the peripheral and central nervous system.[16]

Polypharmacy in Elderly Patients With Cancer

Polypharmacy is most commonly defined as the concomitant use of multiple drugs for the treatment of 1 or more diseases. Alternatively, polypharmacy has been defined as taking at least 1 medication that is not clinically indicated. Polypharmacy has been an important subject in the geriatric literature, and its prevalence ranges from 13% to 92%.[17,18] It has been associated with significantly increased risks for drug interactions, inappropriate prescribing, the development of geriatric syndromes, decreased functional status, and increased health care costs. Patients with cancer are particularly at risk for the effects of polypharmacy; therefore, all medications should be carefully assessed in the oncology clinic.[19] The US National Comprehensive Cancer Network Guidelines for Senior Adult Oncology 2013 state that a review of medications (prescription and over-the counter medications, vitamins, and supplements) and a review for duplication and appropriate use should be performed at every visit to evaluate for PIM use.[20] Patients should specifically be asked about their use of complementary and alternative medications (CAMs) because they may not volunteer this information or recognize the importance of discussing CAMs with the medical team. CAM use was reported by 17% of older adults with cancer and was more common among those who had less advanced disease (ie, those receiving adjuvant, potentially curative treatment) and a higher functional status.[21]

The increased use of medications increases the risk for adverse drug reactions (ADRs). Approximately 5.3% of hospital admissions are associated with ADRs. Higher rates were found in elderly patients, who are likely to be receiving multiple medications for long-term illnesses.[22] In addition, some adverse reactions are identified incorrectly as additional health problems. For example, falls, cognitive deficits, and urinary incontinence are common geriatric syndromes and can either result from a health problem or be a side effect of a medication. When an adverse reaction to 1 drug goes unrecognized or is misinterpreted, it may cause the health care provider to inappropriately prescribe a second drug to treat signs and symptoms, so that a "prescribing cascade" develops.[23] Cashman and colleagues showed that 81% of elderly patients with metastatic cancer were taking 1 or more medications for the treatment or prevention of long-term conditions. More than half of them had moderate or severe drug issues, including taking drugs that were contraindicated, taking doses that needed adjustment for renal or hepatic dysfunction, taking combinations with the potential to exacerbate toxicity, and therapeutic duplication. The authors found that the patients continued to take these medications even if the agents were inconvenient and associated with side effects. In many cases, the benefits of these drugs are likely to be minimal, and medication reviews should be undertaken to address their appropriateness.[24] The treatment of comorbidities for possible long-term benefits may not be realistic in patients with incurable cancer.

Polypharmacy also increases the risk for drug-drug interactions (DDIs). Patients with cancer are at particularly high risk for such interactions because they commonly receive multiple medications, including multiple-drug cytotoxic chemotherapy, hormonal agents, and supportive care drugs. In addition, DDIs in oncology are of particular importance owing to the narrow therapeutic index and the inherent toxicity of anticancer agents. Interactions with other medications can cause small changes in the pharmacokinetics or pharmacodynamics of a chemotherapy agent that may significantly alter its efficacy or toxicity.[25] Sokol and colleagues addressed the issue of polypharmacy and potential DDIs among outpatients in a community setting in the United States by examining the prescribing behavior of oncologists after they had been made aware of potential DDIs.[26] In this study, treating oncologists were encouraged to modify their patients' prescriptions on the basis of reports of potentially interactive drugs. Despite the potential for DDIs, the physicians made no adjustments to the prescriptions.[26]

The CYP system is an important site of DDIs. It consists of more than 50 enzymes responsible for the phase 1 metabolism of many drugs, nutrients, endogenous substances, and toxins. The various CYP isoforms differ in how they are involved in drug metabolism and potentially involved in DDIs. The CYP 3A subfamily (primarily as the CYP 3A4 isoform), which is responsible for the

metabolism of more than 50% of drugs, is involved in several clinically significant DDIs.[27] DDIs are an ongoing concern in the treatment of cancer with targeted therapies, such as tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin (mTOR) inhibitors. The emergence of elderly patients and patients with both cancer and comorbid conditions, leading to polypharmacy, becomes a clinically relevant issue because TKIs and mTOR inhibitors are essentially metabolized by CYP enzymes.[28] For example, the plasma concentration of everolimus (Afinitor, Novartis) was significantly increased by a moderate CYP 3A4 inhibitor (verapamil) in a study of 16 healthy subjects.[29]

Not all DDIs can be predicted, and those that are predictable are not always avoidable. Nevertheless, increased awareness will allow health care providers to minimize the risk by choosing appropriate drugs and monitoring for signs of interaction.[27]

Interventions to Improve Prescribing

Inappropriate prescribing has been defined as the use of medications that introduce a significant risk for an ADE when there exists evidence for an equally or more effective but lower-risk alternative therapy for treating the same medical condition.[30] The identification of PIMs now forms an integral part of policy and practice in the Centers for Medicare & Medicaid Services regulations and are used in Medicare Part D. The use of PIMs is also a quality measure for the National Committee for Quality Assurance (NCQA) Healthcare Effectiveness Data and Information Set (HEDIS).[31] Polypharmacy has been associated with an increased risk for the use of PIMs,[4,32] and ADRs are among the most important consequences of inappropriate prescribing, independently of the number of medications being taken and other confounding factors.[33] There are several ways to evaluate inappropriate prescribing, which have been developed in various settings and have various levels of support for their use.[34] We review here the most widely used.

Medication Appropriateness Index

The medication appropriateness index (MAI) measures the appropriateness of prescribing for elderly patients; 10 criteria are used for each medication prescribed (Table 2). For each criterion, the evaluator rates whether the medication is appropriate, marginally appropriate, or inappropriate. In ambulatory care settings, the MAI has demonstrated feasibility, content validity, predictive validity, and reliability. It has also been shown to predict ADR risk.[35] The main disadvantages are that it takes at least 10 minutes to complete the entire tool and that the tool does not address the underuse of appropriate prescribing.

Table 2. Medication Appropriateness Index Criteria

Is there an indication for the drug?
Is the medication effective for the condition?
Is the dosage correct?
Are the directions correct?
Are the directions practical?
Are there clinically significant drug-drug interactions?
Are there clinically significant drug-disease or drug-condition interactions?
Is there unnecessary duplication with other drugs?
Is the duration of therapy acceptable?
Is this drug the least expensive alternative compared with others of equal usefulness?

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Beers Criteria

In the United States, the Beers criteria are most frequently used as an approach to inappropriate prescribing in the elderly. A consensus guideline, the Beers criteria were first published in 1991 and last updated in 2012.[31] The final updated criteria encompass 53 medications or medication classes, which are divided into 3 categories: PIMs and classes to avoid in older adults, PIMs and classes to avoid in older adults with certain diseases and syndromes that the drugs can exacerbate, and medications to be used with caution in older adults. Table 3 shows some examples of medications to avoid in older adults regardless of diseases or syndromes, and Table 4 summarizes PIMs to be used with caution in older adults. The Beers list is easy to use in clinical and research settings. It can be easily incorporated into computerized decision support systems to prevent inappropriate use, and it can be used in reviews of administrative claims databases to determine the prevalence and predictors of use.[34]

STOPP and START Criteria

The Screening Tool of Older Persons' Prescriptions (STOPP), a newer set of criteria introduced by a panel of European experts, is a validated screening tool for detecting inappropriate prescriptions in older people. It is a reliable and easy-to-use tool, allowing the assessment of prescription drugs often described as inappropriate.[36] The criteria are organized by organ system and include 65 instances of potentially inappropriate prescribing. Table 5 shows some examples of STOPP criteria. The Beers and STOPP criteria have several areas of overlap. Both sets of criteria emphasize the higher risk for ADRs and ADEs in older people with the use of long-acting benzodiazepines, tricyclic antidepressants, anticholinergic drugs, and non–cyclooxygenase 2-selective nonsteroidal anti-inflammatory drugs. Both sets

Table 3. Examples of Medications to Avoid in Older Adults Regardless of Diseases or Syndromes

Medication	Rationale	Recommendations
Antihistamines		
Brompheniramine	Clearance is reduced in advanced age.	Avoid.
Chlorpheniramine Clemastine Cyproheptadine Diphenhydramine (oral) Doxylamine Hydroxyzine Promethazine	There is a greater risk for confusion, hallucinations, sleepiness, blurred vision, difficulty urinating, dry mouth, and constipation.	Use of diphenhydramine for treating severe allergic reactions may be appropriate.
Anti-infective		
Nitrofurantoin (UTIs)	Has potential for pulmonary toxicity; lacks efficacy in patients with CrCl <60 mL/min.	Avoid long-term use. Avoid use in patients with CrCl <60 mL/min.
Cardiovascular drugs		
Doxazosin Prazosin Terazosin	These cause orthostatic hypotension, leading to falls.	Avoid use as antihypertensive agents.
Digoxin >0.125 mg/day	In heart failure, higher dosages have no additional benefit and may increase risk for toxicity.	Avoid.
Spironolactone >25 mg/day	Decreased renal clearance may lead to increased risk for toxic effects. In older adults with heart failure, the risk for hyperkalemia is higher if they are taking >25 mg/day.	Avoid in patients with heart failure or CrCl <30 mL/min.
Cardiovascular drugs: antiarrhythmics		
Amiodarone Dofetilide Dronedarone Flecainide Procainamide Quinidine Sotalol	Data suggest that rate control yields a better balance of benefits and harms than does rhythm control for most older adults. Amiodarone is associated with multiple toxicities (thyroid disease, pulmonary disorders, QT prolongation).	Avoid antiarrhythmic drugs as first-line treatment of atrial fibrillation.
Central nervous system drugs		
TCAs Amitriptyline Imipramine Clomipramine	These are highly anticholinergic, causing sedation and orthostatic hypotension.	Avoid.
Benzodiazepines	All benzodiazepines increase the risk for cognitive impairment, delirium, falls, fractures, and motor vehicle accidents in older adults.	Avoid all benzodiazepines for the treatment of insomnia, agitation, or delirium.
Skeletal muscle relaxants		
Carisoprodol Cyclobenzaprine Metaxalone Methocarbamol	These are poorly tolerated by older adults because of anticholinergic ADRs, sedation, and risk for fractures.	Avoid.

of criteria also focus on several common, potentially adverse drug-disease interactions. However, STOPP criteria PIMs, unlike Beers criteria PIMs, were shown to be significantly associated with avoidable ADEs in older people that cause or contribute to urgent hospitalization.[37]

The Screening Tool to Alert Doctors to the Right Treatment (START) criteria (Table 6) represent the other side of potentially inappropriate prescribing (ie, errors of omission of drug therapy likely to be beneficial to the patient). The advantages of the START and STOPP criteria

Table 3. Examples of Medications to Avoid in Older Adults Regardless of Diseases or Syndromes *(continued)*

Medication	Rationale	Recommendations
Endocrine drugs		
Estrogens with or without progestins	There is evidence of carcinogenic potential (breast and endometrium).	It is acceptable to use low-dose intravaginal estrogen for the management of dyspareunia, UTIs, and other vaginal symptoms.
Megestrol	Minimal effect on weight; increases risk for thrombotic events and possibly death in older adults.	Avoid.
Sulfonylureas, long-duration: Chlorpropamide Glyburide	Glyburide is associated with a higher risk for severe, prolonged hypoglycemia in older adults.	Avoid.
GI drugs		
Metoclopramide	Can cause extrapyramidal effects, including tardive dyskinesia; risk is increased in frail older adults.	Avoid unless used for gastroparesis.
Mineral oil, given orally	There is a potential for aspiration.	Avoid.
Pain medications		
non–COX-selective NSAIDs, oral	Increase risk for GI bleeding and peptic ulcer disease in high-risk groups (>75 years old; taking oral or IV corticosteroids, anticoagulants, or antiplatelet agents). Use of a PPI or misoprostol reduces but does not eliminate risk.	Avoid long-term use unless other alternatives are not effective. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurs in approximately 1% of patients treated for 3 to 6 months and in about 2% to 4% of patients treated for 1 year.

ADR, adverse drug reaction; COX, cyclooxygenase; CrCl, creatinine clearance; GI, gastrointestinal; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; TCA, tricyclic antidepressant; UTI, urinary tract infection.

Adapted from American Geriatrics Society 2012 Beers Criteria Update Expert Panel. *J Am Geriatr Soc*. 2012;60(4):616-631.[31]

are (1) good interrater reliability, (2) the inclusion of medications used both in the United States and in Europe, (3) a logical organization and structure with easy-to-use explicit lists of medication criteria, and (4) the short time required for completion, usually about 3 minutes.[34]

Medication Adherence

The issue of medication adherence is becoming increasingly important in oncology as more cancer therapies are delivered orally. In 2001, one-half of prescriptions dispensed, or 1.5 billion prescriptions, were not taken as directed.[38] Patients who are nonadherent to adjuvant hormonal therapy for breast cancer have worse overall survival than do their adherent counterparts. Suboptimal treatment responses in chronic myeloid leukemia are also associated with poor adherence. Nonadherence can affect clinical trial results, leading to inaccurate assessments of treatment efficacy.[39] A systematic review of the factors determining and influencing medication nonadherence and nonpersistence in patients taking oral anticancer drugs showed that older age is a factor.[40]

Barriers to adherence can occur at the individual, cultural, or system level. Examples of specific barriers are side effects, cost of and access to medication, and individual beliefs about health. A 50-state study of US seniors showed that 27% of seniors who skipped doses or stopped taking a medicine because of side effects or perceived poor efficacy did not tell their physician, and 39% of seniors who reported cost-related nonadherence did not talk with their physicians about it.[41] Strategies to improve adherence are multifactorial and include improvement of patient education, reduction of treatment side effects, interventions to alter behavior, and changes in public policy to improve financial barriers to treatment. Technology has been an effective tool in improving adherence in non–cancer-related illness, and ongoing studies are evaluating its role in the oncology population.[39]

Prescribing Chemotherapy in the Elderly

Evaluation

Chemotherapy in older cancer patients needs to be dosed with care. Older patients have been shown to be more susceptible than younger ones to chemotherapy toxicities, particularly myelosuppression, cardiac toxicity, neuropathy, and mucositis. Other toxicities that can be particu-

Table 4. Potentially Inappropriate Medications To Be Used With Caution in Older Adults

Medication	Rationale	Recommendations
Aspirin for primary prevention of cardiac events	Evidence of benefit is lacking in individuals ≥80 years old.	Use with caution in persons ≥80 years old.
Dabigatran	The risk for bleeding is increased compared with warfarin in adults ≥75 years old; evidence is lacking for efficacy and safety in patients with CrCl <30 mL/min.	Use with caution in adults ≥75 years old or if CrCl <30 mL/min.
Antipsychotics Carbamazepine Carboplatin Cisplatin Mirtazapine SNRIs SSRIs TCAs Vincristine	May exacerbate or cause SIADH or hyponatremia; sodium level must be monitored closely when dosage is started or changed in older adults because of increased risk.	Use with caution.

CrCl, creatinine clearance; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; TCA, tricyclic antidepressant.

Adapted from American Geriatrics Society 2012 Beers Criteria Update Expert Panel. *J Am Geriatr Soc*. 2012;60(4):616-631.[31]

Table 5. Examples of STOPP Criteria

Cardiovascular system	
Digoxin	Long-term use >125 µg/day in patients with renal dysfunction
Loop diuretic	For dependent ankle edema only (no signs of heart failure); compression hosiery usually more appropriate
Thiazide diuretic	With history of gout (may exacerbate gout)
Noncardioselective β-blocker	With COPD (risk for increased bronchospasm)
Diltiazem or verapamil	With NYHA class III or IV heart failure (may worsen heart failure)
Calcium channel blocker	With chronic constipation (may exacerbate constipation)
Warfarin	For first uncomplicated DVT >6 months For first uncomplicated pulmonary embolus >12 months (no proven benefit)
Central nervous system and psychotropic drugs	
TCAs	With dementia (risk for worsening cognitive impairment)
SSRIs	With hyponatremia
Gastrointestinal system	
PPIs	For peptic ulcer disease at full therapeutic doses for >8 weeks
NSAIDs	With moderate to severe hypertension or heart failure

COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis; NYHA, New York Heart Association; PPI, proton pump inhibitor; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor; STOPP, Screening Tool of Older Person's Prescriptions; TCA, tricyclic antidepressant.

Adapted from Gallagher P et al. *Int J Clin Pharmacol Ther*. 2008;46(2):72-83.[36]

larly troublesome include nausea, vomiting, and diarrhea. The control of these complications is essential to improve outcome and to maintain quality of life and independence. Because older patients have been underrepresented in clinical trials, there has been a lack of evidence-based data to make meaningful clinical decisions. However, a number of simple guidelines can be followed to allow the safe and effective administration of therapy. The goals of therapy must be clearly defined. Is the treatment curative in intent, or is it palliative? The answer to this question will help guide dosing. The patient undergoing curative treatment should receive standard doses according to schedules that are part of an established regimen. Dose modification is acceptable to accommodate relevant factors, such as end-organ dysfunction. The patient undergoing palliative treatment should also receive standard regimens, but because the goals of treatment are to alleviate symptoms and maintain quality of life, the dosing

Table 6. Examples of START Criteria

Medication	Recommendation
Warfarin	In chronic atrial fibrillation
Aspirin	In chronic atrial fibrillation when warfarin is contraindicated
Antihypertensive therapy	Systolic blood pressure consistently >160 mm Hg
Statin	History of coronary, cerebral, or peripheral vascular disease, when patient is functionally independent for activities of daily living and life expectancy >5 years
ACEI	With chronic heart failure Following acute myocardial infarction
β-Blocker	With chronic stable angina
Bisphosphonate	With maintenance corticosteroid therapy
Calcium and vitamin D	Osteoporosis (fragility fracture, acquired dorsal kyphosis)
Antiplatelet agent	In diabetes mellitus with major cardiovascular risk factors (hypertension, hypercholesterolemia, smoking history)

ACEI, angiotensin-converting enzyme inhibitor; START, Screening Tool to Alert Doctors to Right Treatment.

Adapted from Gallagher P et al. *Int J Clin Pharmacol Ther*. 2008;46(2):72-83.[36]

regimens need to be modified to try to avoid toxicity but still provide a potentially efficacious dose.

The general status of the geriatric patient plays a crucial role in treatment. It has been well described that standard oncology measures such as the Karnofsky Performance Status score and the Eastern Cooperative Oncology Group score are not adequate as the sole evaluation of the status of elderly patients with cancer.[42] A more in-depth assessment needs to be performed. A number of studies have been done to aid the clinician in evaluating older patients. The Comprehensive Geriatric Assessment, which is performed by geriatricians, was not designed to be predictive. It is a tool to define specific geriatric clinical problems that would not otherwise be detected in a routine history and physical. Two oncology-specific modified Comprehensive Geriatric Assessments have been shown to be predictive in the older population. A prospective evaluation of the Cancer and Aging Research Group trial showed that severe toxicity can be predicted from easily obtained clinical factors.[43] The predictive model that was developed includes age older than 71 years, polychemotherapy, creatinine clearance rate below 35 mL/min, hemoglobin level below 11 g/dL, decreased hearing, falls, social isolation, limited activity, and deficiency in instrumental activities of daily living. A study by Extermann and colleagues also demonstrated that chemotherapy toxicity can be predicted in an older population based on instrumental activities of daily living and other easily obtained clinical information.[44] Prediction models needs to be evaluated prospectively in disease-specific therapy as well as in curative and palliative treatment. Patients who meet the definition of frailty are unlikely to benefit from chemotherapy, and palliative treatment may be the most appropriate for them.[45,46]

Pharmacology

The clinician needs understand the pharmacokinetics of the drugs being prescribed and the patient's physiology.[47,48] Few prospective trials of chemotherapy have been undertaken in older patients.[49] Most changes in pharmacokinetics are due to end-organ dysfunction. The most important measurement is the determination of kidney function in patients taking drugs that have significant renal clearance. There are age-related changes in excretory function. As described earlier, there is a gradual loss in renal mass and a decline in function with age. This loss is primarily due to loss of cortical mass with relative preservation of the renal medulla.[11] Glomerular sclerosis results in a loss of capacity to perform the ultrafiltration of plasma, which leads to a decrease in the glomerular filtration rate of approximately 1 mL/min for every year past the age of 40 years. The reduction in the glomerular filtration rate is not always reflected by an increase in serum creatinine levels because of the simultaneous loss of muscle mass that occurs with age. It should be noted that many older patients whose serum creatinine level is within the normal range for a particular laboratory have renal insufficiency.[50] In order to facilitate the estimation of glomerular clearance, various equations have been evaluated to calculate creatinine clearance based on the serum creatinine level and other factors. Two equations frequently used clinically by oncologists are the Cockcroft-Gault and Jelliffe equations.[51,52] Unfortunately, these equations are less accurate in certain populations, such as patients who have severe renal failure or decreased muscle mass, patients who are obese, and the elderly. Most individuals lose muscle mass with age. Therefore, a low serum creatinine level of less than 1 mg/dL may represent diminished muscle mass and diminished production of creatinine rather than exceptional renal function. Dosing

modifications of chemotherapeutic agents based on these physiologic declines have been suggested.[53,54] Dosing recommendations for older patients and those with renal insufficiency have been published.[12,50,55-58]

Toxicity

In certain cases, toxicities may be mitigated with various interventions. The use of colony-stimulating factors may markedly reduce the period of myelosuppression associated with myelosuppressive chemotherapy and has increased the therapeutic ratio of standard doses of chemotherapy for elderly. Guidelines from international societies have been published.[59,60] Hematopoietic support has shifted the focus of toxicity from myelosuppression to nonhematologic toxicity. Examples of nonhematologic toxicity include diarrhea associated with irinotecan, and neuropathy associated with oxaliplatin and paclitaxel.[61] Cardiac toxicity needs to be carefully evaluated, particularly with the use of doxorubicin and trastuzumab (Herceptin, Genentech). The spectrum of toxicity in an elderly patient may be different from that in a younger patient. Schedule and formulation changes may allow potentially toxic agents to be used in the elderly population. The common toxicity criteria as currently used may not be adequate to assess adverse events in elderly patients. For example, an assessment for neuropathy should include an evaluation of functional decline or falls. The reporting of clinical trials should also be elder-specific. Most trials report only grade 3 or 4 toxicity, but grade 2 toxicity in an older patient has clinical relevance. It will help clinicians in their decision making if they know the full spectrum of toxicity.[62,63]

The evaluation and treatment of the older patient with cancer represents the ultimate in personalized medicine. Because of the heterogeneity of the older population, some form of geriatric evaluation is required. The treatment plan, including the goals of treatment and the dosing of chemotherapy, needs to be carefully defined. Implementing these measures is the best way to avoid toxicity and allow the patient to benefit from treatment.

Concluding Remarks

To prescribe appropriately, we need to consider not only the pharmacologic properties of drugs, but also clinical, epidemiologic, social, cultural, and economic factors. Appropriate prescribing should include a consideration of life expectancy and the potential benefits and goals of care. Most of all, this paper highlights the importance of evaluating the appropriateness of medications during each assessment of the older patient with cancer, and it provides tools to help determine PIMs in order to prevent adverse events that can impact treatment outcomes and quality of life.

Disclosures

The authors have no relevant conflicts of interest to disclose.

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