Journal of Geriatric Oncology 10 (2019) 4–30

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

Review article

Clinical pharmacology of oncology agents in older adults: A comprehensive review of how chronologic and functional age can influence treatment-related effects

Ginah Nightingale [a,*], Rowena Schwartz [b], Ekaterina Kachur [c], Brianne N. Dixon [d], Christine Cote [e], Ashley Barlow [a], Brooke Barlow [a], Patrick Medina [f]

[a] Department of Pharmacy Practice, Jefferson College of Pharmacy, Thomas Jefferson University, Philadelphia, PA, United States
[b] Pharmacy Practice, James L. Winkle College of Pharmacy, University of Cincinnati, Cincinnati, OH, United States
[c] Department of Hematologic Oncology & Blood Disorders, Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, United States
[d] Department of Pharmacy, Memorial Sloan Kettering Cancer Center, New York, NY, United States
[e] Merck, North Wales, PA, United States
[f] Director of Pharmacy, Stephenson Cancer Center, University of Oklahoma, Oklahoma City, OK, United States

ARTICLE INFO

Article history:
Received 3 October 2017
Received in revised form 11 May 2018
Accepted 19 June 2018
Available online 13 July 2018

Keywords:
Pharmacology
Pharmacodynamics
Pharmacokinetics
Geriatric assessment
Comorbidity
Functional status
Cognitive impairment
Polypharmacy
Chemotherapy toxicity

ABSTRACT

Unique challenges exist when managing older adults with cancer. Associations between cancer and age-related physiologic changes have a direct impact on pharmacokinetics and pharmacodynamics of cancer therapies and can affect drug dosing, dose intensity, efficacy, safety and quality of life. The breadth and depth of these issues, however, have not been fully evaluated because the majority of clinical trials have focused on a younger and healthier population. As a consequence, little information is available to support clinicians in making evidence-based decisions regarding treatment with cancer therapies in older adults, especially those over age 75. Prior clinical pharmacology reviews summarized the literature on how age-related physiologic changes can influence and affect conventional and targeted anti-cancer treatments. Our article provides an updated review with expanded information that includes small molecule kinase inhibitors, monoclonal antibodies, immunotherapies, hormonal, conventional, and miscellaneous agents. Additionally, our article integrates how functional age, determined by the geriatric assessment (GA), can also influence treatment-related effects and health outcomes. Broadening cancer therapy trials to capture not only chronologic age but also functional age would allow clinicians to better identify subsets of older adults who benefit from treatment versus those most vulnerable to morbidity and/or mortality.

Contents

* Corresponding author at: Jefferson College of Pharmacy, Thomas Jefferson University, 901 Walnut Street Suite 946, Philadelphia, PA 19107, United States
E-mail address: ginah.nightingale@jefferson.edu (G. Nightingale).

https://doi.org/10.1016/j.jgo.2018.06.008
1879-4068/

1. Introduction

More than 14 million Americans are living with a cancer diagnosis, and an estimated 1.7 million new cases of cancer are diagnosed each year [1]. The median age at diagnosis is 66 years [1]. Older adults (≥65 years of age) have increased comorbidity, diminished physiological reserves, reduced functional capacity, polypharmacy, geriatric syndromes and age-related physiologic changes. Because such factors may influence drug dosage, dose intensity, and treatment-related efficacy and toxicity, clinical cancer trials typically enroll a younger and healthier population and exclude older adults. As a result, older individuals are underrepresented in clinical registration trials and the National Cancer Institute's National Clinical Trials Network even though most new cases of cancer occur in this population [1–4]. This practice has resulted in a lack of data available for clinicians to make evidence-based treatment decisions regarding cancer therapies in older adults, especially those over age 75.

The Institute of Medicine reported in 2013 that the lack of evidence in older adults ultimately undermined the quality of cancer care provided to this population [5]. The report, "*Delivering High-Quality Cancer Care: Charting a Course for a System in Crisis*", emphasized the need for evidence-based information through strategies such as [1] matching the characteristics of the study population to reflect the individuals with the disease, and [2] increasing the depth of data by capturing a more detailed characterization of this population, such as by utilizing a geriatric assessment tool [5]. The American Society of Clinical Oncology has also recognized the importance of evaluating new drug therapies in the older adult with cancer and has published recommendations to improve the generation of evidence for treating older adults with cancer [6].

Certainly, chronologic age and age-related physiologic changes provide useful means to measure the effects of cancer therapies. In order to get a clearer assessment of how cancer therapies affect older adults, surrogate measures should also be assessed and evaluated, specifically the domains of the comprehensive geriatric assessment (CGA) [7–8]. The CGA is a multidimensional, inter-professional process that applies validated tools to determine an older adult's medical, functional and psychosocial capability in order to develop a coordinated and integrated plan for treatment and long-term follow up [9]. Prior reviews summarized the literature on how age-related physiologic changes can influence and affect conventional and targeted anti-cancer treatments [10–11]. Our article provides an updated review of the evidence on how age-related physiologic changes can influence and affect oncology treatments, including small molecule kinase inhibitors, monoclonal antibodies, immunotherapies, hormonal, conventional, and miscellaneous agents. Our article additionally integrates how functional age, determined by the GA, can influence and affect treatment-related toxicity, efficacy and health outcomes in the older adult oncology population.

2. Age-Related Physiologic Changes and Influence on Oncology Pharmacology

The process of aging involves continuous regression of functional reserves and affects multiple organs and organ systems. These age-related physiologic changes can affect the pharmacokinetics and pharmacodynamics of oncology drug treatments in a variety of ways.

2.1. Pharmacokinetics

Pharmacokinetics is defined as the time course of a drug (and/or drug metabolites) throughout the body with regard to absorption, distribution, metabolism, and excretion/elimination [12]. Pharmacokinetic drug absorption in older adults can be affected by non-modifiable factors including reduced gastric acid secretion, gastric emptying, peristalsis, splanchnic blood flow and a smaller bowel surface area [13]. Modifiable factors that considerably affect drug absorption in this population include polypharmacy and concomitant medication use with drugs that alter absorption of oncology agents (e.g., erlotinib absorption can be significantly reduced by proton pump inhibitors such as omeprazole) [13]. These types of gastrointestinal physiologic changes have the potential to generate significant concern with the exponential growth and expansion of oral oncology therapies.

Body composition changes that occur in this population can also play a role. A decline in total body water may decrease volume distribution of hydrophilic drugs (e.g., fluorouracil). An increase in body fat may increase volume distribution of lipophilic drugs (e.g., irinotecan), prolonging half-life and increasing time to elimination [13–14].

Older age is also associated with a decrease in hepatic volume, hepatic blood flow, and reduced clearance of drugs metabolized by the liver through the type I pathway of reactions (e.g., oxidative, reduction reactions and hydrolysis) by the enzymes of the cytochrome *p*450 (CYP) pathway system [14–15]. A more robust discussion of the impact of age on hepatic metabolism can be found in an article by Schmucker [15]. Cancer therapies that are metabolized by the liver (e.g., irinotecan is metabolized to SN-38, the active metabolite which exerts antitumor activity) may enhance toxicity or diminish efficacy in patients with liver impairment [16]. Recommendations for hepatic dosage modifications utilize the Child-Pugh score, an FDA classification for determining dosage adjustments based on five clinical measures of hepatic impairment: ascites, total bilirubin, albumin, prothrombin time and the presence of encephalopathy [17].

Some of common medications that older adults take may inherently predispose them to pharmacokinetic drug interactions [18–20]. Such pharmacokinetic drug interactions may result from enzyme induction or inhibition caused by a combination of drugs. Drug interactions involving the CYP pathway can occur when a substance (e.g., drug, food, herbal supplement) being administered at the same time as the cancer therapy alters the intended therapeutic effect or safety of a drug [21–23]. For example, abiraterone acetate, a novel anti-androgen used for advanced prostate cancer, has major CYP450 enzyme activity (specifically CYP3A4, CYP2D6) which can lead to clinically relevant drug interactions when used with drugs that induce or inhibit CYP450 metabolism. Concurrent use of abiraterone acetate with a strong CYP3A4 inducer, such as phenytoin, may lead to decreased abiraterone acetate serum concentration and diminished efficacy [24]. Conversely, concurrent use of abiraterone acetate with a major CYP2D6 substrate, such as metoprolol, may lead to an increased serum concentration of the CYP2D6 substrate and subsequent metoprolol toxicity manifested as sinus bradycardia, hypotension, and falls [24].

Drug elimination and clearance refers to a drug's final route of exit from the body, which may involve active metabolites excreted through the biliary system, the kidneys, or the stool, among other pathways [14–15]. Aging is associated with a decline in renal mass by approximately 25%–30% overall, and each year after the fourth decade of life, renal blood flow declines by about 1%, with a continuous average decline of 10% per decade [12]. This reduction in glomerular filtration rate may lead to enhanced toxicity of oncology agents, particularly those with significant renal clearance (e.g., cisplatin, methotrexate). A variety of renal function calculation equations exists, but the Cockcroft–Gault formula is the most practical for dosage modifications in the setting of renal impairment [25].

2.2. Pharmacodynamics

Age-related physiologic changes also affect the pharmacodynamics of oncology drug treatments in a variety of ways. Pharmacodynamics is defined as the correlation between drug concentration at the site of action and the resulting effect, including the time course and intensity of therapeutic and adverse effects [12]. The pharmacodynamics of a drug is determined by the concentration of the drug at the receptor and by drug-receptor interactions (e.g., variations in receptor number, receptor affinity, second messenger response, and cellular response),

Table 1
Summary of small molecule kinase inhibitors used in older adults with cancer.

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
Anaplastic lymphoma kinase (ALK) inhibitors				
Alectinib [28–30]	No adjustment required for mild to moderate renal impairment. Has not been studied in patients with severe renal impairment (CrCl <30 mL/min) and/or end stage renal disease (ESRD)	No adjustment required for pre-existing mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin >1.0 to 1.5 times ULN and any AST). Has not been studied in patients with pre-existing moderate or severe hepatic impairment	Two phase 3 clinical trials, J-ALEX and ALEX, compared the efficacy and safety of alectinib and crizotinib for non-small cell lung cancer (NSCLC). In ALEX, the median age was 54 years (range 18–91) in crizotinib group and 58 years (range 25–88) in alectinib group. Alectinib group achieved significantly higher progression free survival (12-month event-free survival rate, 68.4% [95% CI, 61.0 to 75.9] with alectinib vs. 48.7% [95% CI, 40.4 to 56.9] with crizotinib (HR = 0.47, 95% CI, 0.34–0.65; $p < .0001$). The superiority was maintained when compared among younger (<65 years) and older (≥65 years) patients, and no information was noted regarding safety differences between groups	Polypharmacy: Avoid concomitant use with other bradycardia causing agents, if possible Nutrition: Take medication with food. High fat, high-calorie meal increases exposure to alectinib and its active metabolite by 3.1-fold
Brigatinib [31–32]	No adjustment required for mild to moderate renal impairment. Has not been studied in patients with severe renal impairment (Creatinine Clearance [CrCl] < 30 mL/min) and/or ESRD	No adjustment required for pre-existing mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin >1.0 to 1.5 times ULN and any AST). Has not been studied in patients with pre-existing moderate or severe renal impairment	A phase 2 clinical trial, ALTA, compared c the efficacy and tolerability of brigatinib in 222 patients with NSCLC. In the study, 19.4% of patients were aged 65–74 and 4.1% were aged ≥75 years. No difference in efficacy or safety was noted between younger and older patients	Polypharmacy: Avoid concomitant use with other bradycardia causing agents, if possible Brigatinib may decrease effects of antidiabetic and antihypertensive agentsAvoid concomitant use with strong cytochrome-3A (CYP3A) inhibitors, if possible. If co-administration is necessary, reduce brigatinib dose by ~ 50%. Avoid concomitant use with strong CYP3A inducers and major CYP3A substrates, if possible
Ceritinib [33]	No adjustment required for mild to moderate renal impairment Has not been studied in patients with severe renal impairment (CrCl <30 mL/min) or ESRD	No adjustment required for pre-existing mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin >1.0 to 1.5 times ULN and any AST). Has not been studied in patients with pre-existing moderate or severe hepatic impairment	Of the 925 patients in clinical trials, 18% were ≥65 years old and 5% were ≥75 years old. No difference in efficacy or safety was noted between younger and older patients	Polypharmacy: Avoid concomitant use with other bradycardia causing and/or QTc-prolonging agents, if possible Avoid concomitant use with strong CYP3A inhibitors, if possible. If co-administration is necessary, reduce ceritinib dose by ~ 1/3 (round to the nearest 150 mg). Avoid concomitant use with strong CYP3A inducers and major CYP3A and CYP2C9 substrates, if possible Nutrition: Take medication on an empty stomach
Crizotinib [34–35]	No adjustment required for mild to moderate renal impairment Reduce dose to 250 mg orally once daily in patients with severe renal impairment (CrCl <30 mL/min) not requiring dialysis	Has not been studied in patients with pre-existing hepatic impairment	Of the 1669 ALK-positive NSCLC patients in clinical trials, 16% were ≥65 years old and 3.8% were ≥75 years old. No difference in efficacy or safety was noted between younger and older patients Blackhall et al. compared the safety of crizotinib in older (≥65 years old) versus younger patients. A higher incidence of adverse effects was identified in the elderly (15 vs. 7%) but was not statistically significant	Polypharmacy: Avoid concomitant use with other bradycardia- causing and/or QTc-prolonging agents, if possible Avoid concomitant use with strong CYP3A inhibitors and/or inducers, and major CYP 3A substrates, if possible
BCR-abl inhibitor				
Bosutinib [36–37]	No adjustment required for pre-existing mild renal impairment (CrCl >50 to 80 mL/min). Reduce initial dose to 400 mg once daily for moderate renal impairment (CrCl 30 to 50 mL/min). Reduce initial dose to 300 mg once daily for severe renal impairment (CrCl <30 mL/min)	Reduce initial dose to 200 mg once daily for mild to severe pre-existing hepatic impairment (Child-Pugh Class A, B, or C)	In clinical trials comparing bosutinib with imatinib in chronic myelogenous leukemia (CML), 20% of patients were aged ≥65 and 4% were aged ≥75 years old. No difference in efficacy or safety was noted between younger and older patients	Polypharmacy: Avoid concomitant use with QTc-prolonging agents, if possible Avoid concurrent use with strong or moderate CYP3A4 inhibitors or inducers, if possible Avoid concurrent use with proton pump inhibitors. Separate dosing of H2-receptor antagonists or antacids by at least 6 h Nutrition: Take medication with food
Dasatinib [38–39]	No adjustment required for pre-existing mild to severe renal impairment (has not been studied)	No adjustment required for pre-existing mild to severe hepatic impairment (Child-Pugh Class A, B, or	Of the 2712 patients enrolled in clinical trials, 23% were ≥65 and 5% were ≥75 years old. No difference in	Polypharmacy: Avoid concurrent use with antiplatelet and anticoagulant agents due to risk of hemorrhage

Table 1 (*continued*)

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
		C)	efficacy (confirmed Complete Cytogenetic Response (cCCyR) and major molecular response (MMR)) was noted between younger and older patients. Older patients were more likely to experience weakness, pleural and pericardial effusion, diarrhea, edema, gastrointestinal hemorrhage, abdominal distention, heart failure, hypertension, pulmonary and weight loss	
			Latagliata et al. retrospectively analyzed outcomes of dasatinib therapy in 125 elderly patients (> 60 years old) who were resistant or intolerant to imatinib. Median age was 69 years. Forty percent of patients had 2 or more comorbidities, mostly hypertension and cardiovascular diseases. Dasatinib showed good efficacy with 59.1% achieving cytogenetic response (9.8% partial and 49.3% complete). Four-year overall survival was 84.2%. Hematological grade 3/4 toxicity was reported in 31% of patients and 27% experienced non-hematologic toxicity (e.g., pleural and pericardial effusion)	Avoid concurrent use with strong CYP3A4 inhibitors. If unavoidable, reduce dasatinib from 100 mg once daily to 20 mg daily or from 140 mg once daily to 40 mg daily Avoid concurrent use with proton pump inhibitors or H2-receptor antagonists. Separate dosing of antacids by at least 2 h
Imatinib [40–42]	Maximum recommended dose for patients with mild renal impairment is 600 mg/day (CrCl 40 to 59 mL/min). Reduce by 50% for patients with moderate renal impairment (CrCl 20 to 39 mL/min) with maximum recommended of 400 mg daily. Use caution in patients with severe impairment (CrCl <20 mL/min). Small number of patients with severe impairment have tolerated 100 mg daily	No adjustment required for pre-existing mild to moderate hepatic impairment. Reduce dose by 25% in patients with pre-existing severe hepatic impairment	In CML clinical trials, about 20% of CML patients enrolled in imatinib trials were aged ≥65 years. Among GIST patients, 16% of enrolled in the unresectable or metastatic study and 31% enrolled in the adjuvant study were aged ≥65 years old. No difference in efficacy was noted between younger and older patients	Polypharmacy: Avoid concurrent use with strong CYP3A4 CYP3A4 inhibitors and inducers. If unavoidable, increase imatinib dose by ~50%
			Latagliata et al. retrospectively analyzed outcomes of 211 chronic-phase CML patients aged >75 years and many had comorbidities. Dose reductions were required in 44.5% of patients and 12.7% discontinued treatment due to toxicity	
			Iurlo et al. evaluated the effects of polypharmacy on outcomes of imatinib therapy in a retrospective analysis of 296 CML patients aged >75 years. Polypharmacy was reported in 107 patients (36.1%). No statistical difference was found in the dose reductions, cytogenetic and molecular responses, hematological and non-hematological toxicity among patients with versus without polypharmacy	Imatinib may enhance the anticoagulant effect of warfarin so an alternative anticoagulant is recommended
Nilotinib [43–45]	No adjustment required for pre-existing mild to severe renal impairment (has not been studied with serum creatinine (SrCr) > 1.5 times UNL)	Patients with pre-existing mild to severe hepatic impairment (Child-Pugh Class A, B, or C) should have initial nilotinib dose reduction from 300 mg twice daily to 200 mg twice daily for new diagnosis of Ph + CML. Patients with resistant or intolerant CML and pre-existing mild to moderate impairment (Child-Pugh class A or B) should have initial nilotinib dose reduced to 300 mg twice daily and patients with severe impairment (Child-Pugh C) to 200 mg twice daily	Clinical trials evaluating nilotinib for newly diagnosed and resistant/intolerant patients with CML included 12% and 30% of patients ≥65 years old. No difference in major cytogenetic response rate was noted between younger and older patients. No major difference in safety was noted between younger and older age groups	Polypharmacy: Avoid concomitant use with QTc-prolonging agents, if possible Avoid concurrent use with strong CYP3A4 inhibitors. If unavoidable, reduce nilotinib dose from 300 mg twice daily to 200 mg once daily or 400 mg twice daily to 300 mg once daily. Avoid concurrent use with strong CYP3A4 inducers. Increase in nilotinib dose is unlikely to counterbalance reduced exposure Avoid concurrent use with proton pump inhibitors. H2-receptor antagonists may be given at least 10 h before and 2 h after nilotinib. Separate dosing of antacids by at least 2 h before or after nilotinib

(*continued on next page*)

Table 1 (*continued*)

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
				Nutrition: Take medication on an empty stomach. Electrolyte imbalances (magnesium, potassium) should be corrected prior to initiation and during therapy
Ponatinib [46–47]	No dosage adjustments provided for patients with pre-existing renal impairment (has not been studied)	Reduce initial dose to 30 mg once daily for mild to severe pre-existing hepatic impairment (Child-Pugh Class A, B, or C)	In a phase 2 trial involving 449 patients, 35% were aged ≥65 years. No difference in hematologic response rate was observed among older and younger patients with accelerated or blast phase CML and Ph + ALL. Older patients with chronic phase CML had a lower major cytogenetic response rate compared to younger patients (40% vs 65%, respectively). Older patients were more prone to adverse events including vascular occlusion, thrombocytopenia, weakness, decreased appetite, dyspnea, and peripheral edema. Cardiovascular toxicity was dose dependent with older age and cardiovascular risk factors	Comorbidities: Caution should be used in patients with existing cardiovascular disease, hypertension, diabetes, and hyperlipidemia due to increased risk of arterial occlusive events Polypharmacy: Avoid concurrent use with strong CYP3A4 inhibitors. If unavoidable, reduce ponatinib dose to 30 mg daily. Avoid concurrent use with strong CYP3A inducers, if possible
BRAF inhibitors				
Dabrafenib [48–49]	No adjustment required for pre-existing mild-severe renal impairment (has not been studied)	No adjustment required for pre-existing hepatic impairment	In a population pharmacokinetics trial, ~22% of patients were ≥ 65 years of age. No difference in efficacy or safety was noted between younger and older patients	Polypharmacy: Avoid concurrent use with strong CYP3A4 inhibitors and inducers and inhibitors, if possible Nutrition: Take medication on an empty stomach
Vemurafenib [50–52]	No adjustment required for pre-existing mild-severe renal impairment (has not been studied)	No adjustment required for pre-existing mild-severe hepatic impairment (has not been studied)	Zhang et al. conducted a pharmacokinetics study of vemurafenib and ~24% of patients were aged ≥65 years of age. No major differences in effectiveness or safety were observed but older patients may be at an increased risk for adverse effects Larkins et al. conducted a study and found an increased incidence of atrial fibrillation, keratoacanthoma, peripheral edema, and nausea/decreased appetite in older adults	Polypharmacy: Avoid concurrent use with agents that are metabolized by CYP1A2, CYP2D6 and CYP3A4
Epidermal growth factor receptor (EGFR) inhibitors				
Afatinib [53–55]	No adjustment required for pre-existing mild to moderate renal impairment (eGFR >30 mL/min/1.73 m^2). Reduce dose to 30 mg once daily for pre-existing eGFR 15 to 29 mL/min/1.73 m^2). Has not been studies in eGFR <15 mL/min/1.73 m^2 and hemodialysis	No adjustment required for pre-existing mild to moderate hepatic impairment (Child-Pugh Class A or B). Has not been studies in severe impairment (Child-Pugh Class C)	In the LUX-lung 3 and LUX-lung 6 phase 3 trials, 220 elderly patients (≥65 years old) were included in analysis, 134 in LUX-Lung 3 and 86 in LUX-Lung 6, respectively. Overall survival was similar among elderly patients treated with afatinib versus chemotherapy	Polypharmacy: If concomitant therapy with a P-glycoprotein inhibitor is not tolerated, reduce afatinib daily dose by 10 mg. If patients require concomitant chronic therapy with a P-glycoprotein inducer, increase afatinib dose by 10 mg Nutrition: Take medication on an empty stomach. Administration with high-fat meal decreases systemic exposure
Erlotinib [56–58]	No dosage adjustments provided for patients with pre-existing renal impairment (has not been studied)	No adjustment required for pre-existing hepatic impairment (Child-Pugh Class A, B or C). Risk of hepatic toxicity is increased in patients with pre-existing hepatic impairment	Of the 1297 patients included in erlotinib clinical trials, 40% were aged ≥65 and 10% were aged ≥75 years. No difference in efficacy was noted between younger and older patients Wheatley-Price et al. reported more overall and severe toxicity among aged ≥70 years versus younger patients (35% vs 18%, $p < .001$) Yamada et al. conducted a phase 2 trial and reported comparable efficacy outcomes between older and younger patients. A higher percentage of elderly patients (≥ 75 years old) required erlotinib dose reduction (32.5%) as compared to the general population	Polypharmacy: Avoid concurrent use with strong CYP3A4 and CYP1A2 inhibitors. If severe reactions occur, reduce erlotinib daily dose by 50 mg decrements Avoid concurrent use with proton pump inhibitors. Separate dosing with H2-receptor antagonists by administering erlotinib 10 h after and at least 2 h before the next dose of the H2-receptor antagonist Erlotinib may increase INR and bleeding risk in patients on concomitant coumarin-derived anticoagulants Nutrition: Take medication on an empty stomach
Lapatinib [59–61] (has	No adjustment required for pre-existing mild to severe renal impairment (has not been studied)	No adjustment required for pre-existing mild to moderate hepatic impairment (Child-Pugh Class A or B).	Of 198 patients enrolled in lapatinib plus capecitabine trials, 17% was ≥65 and 1% was ≥75 years old. Among 642	Polypharmacy: Avoid concomitant use with QTc-prolonging agents, if possible

Table 1 (*continued*)

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
HER2-neu activity)		Patients with pre-existing severe hepatic impairment (Child-Pugh Class C) should have lapatinib dose reduction from 1250 mg/day to 750 mg/day or from 1500 mg/day to 1000 mg/day	patients enrolled in lapatinib plus letrozole trials, 44% were ≥ 65 and 12% were ≥ 75 years old. No difference in efficacy or safety was noted between younger and older patients A pooled analysis of eleven phase 1, 2 and 3 clinical trials in patients treated with lapatinib showed a greater incidence of grade 3 diarrhea in patients aged >70 years compared to younger patients (33% vs. 19%)	Avoid concurrent use with strong CYP3A4 inhibitors. If unavoidable, reduce lapatinib to 500 mg orally once daily Avoid concurrent use with strong CYP3A4 inducers, if possible. If unavoidable, gradually titrate lapatinib from 1250 mg once daily up to 4500 mg daily or from 1500 mg once daily up to 5500 mg daily as tolerated Nutrition: Take medication on an empty stomach
Vandetanib [62–63] (has VEGF activity)	Reduce initial dose to 200 mg orally once daily for patients with CrCl <50 mL/min. No adjustment provided for ESRD requiring dialysis (has not been studied)	No adjustment provided in package insert for pre-existing mild hepatic impairment (Child-Pugh Class A).\ Not recommended for patients with pre-existing moderate to severe hepatic impairment (Child-Pugh Class B or C)	Gridelli et al. conducted a phase 2 trial and assessed efficacy and safety of vandetanib with gemcitabine compared to gemcitabine alone for treatment of 124 elderly patients (>70 years old) NSCLC. The vandetanib and gemcitabine combination significantly prolonged progression free survival compared to gemcitabine alone, but no statistically significant differences were observed in objective response rate and overall survival. Pyrexia, dyspnea, and neutropenia were the most common toxicities and occurred at similar rate between two arms	Polypharmacy: Avoid concomitant use with QTc-prolonging agents, if possible. Do not initiate therapy if QTc > 450 msec Avoid concurrent use with strong CYP3A4 inhibitors or inducers Nutrition: Electrolyte imbalances (magnesium, potassium, calcium) should be corrected prior to initiation and during therapy
Mitogen-activated protein kinase (MEK) inhibitors				
Cobimetinib [64]	No adjustment required for pre-existing mild-severe renal impairment (has not been studied)	No adjustment required for pre-existing mild (Child-Pugh A), moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment	Clinical trials with cobimetinib did not include sufficient numbers of patients aged ≥65 years to determine if efficacy and safety differences exist between older and younger patients	Polypharmacy: Avoid concurrent use with strong or moderate CYP3A4 inhibitors. If concurrent short-term use (≤ 14 days) cannot be avoided, reduce the cobimetinib dose from 60 mg to 20 mg
Trametinib [65]	No adjustment required for pre-existing mild-severe renal impairment (has not been studied)	No adjustment required for pre-existing mild-severe hepatic impairment (has not been studied)	Clinical trials with trametinib did not include sufficient numbers of patients aged ≥65 years to determine if efficacy and safety differences exist between older and younger patients	Polypharmacy: Avoid concurrent use of strong inhibitors or inducers of CYP3A4 or CYP2C8 Nutrition: Take medication on an empty stomach
Vascular endothelial growth factor (VEGF) inhibitors				
Axitinib [66–67]	No adjustment required for pre-existing mild-severe renal impairment (has not been studied)	No adjustment necessary for mild impairment (Child-Pugh Class A). For moderate impairment (Child-Pugh Class B): reduce starting dose by ~50%. Has not been studied in severe impairment (Child-Pugh Class C)	Miyake et al. conducted a trial and ~34% of patients were aged ≥65 years. No overall differences in safety and efficacy were observed between younger and older patients	Polypharmacy: Avoid concomitant use of strong CYP3A4 inhibitors. If concomitant administration with a strong CYP3A4 inhibitor cannot be avoided, ~50% dosage reduction is recommended
Cabozantinib [68]	No adjustment required for pre-existing mild-severe renal impairment or dialysis (has not been studied)	Mild or moderate impairment (Child-Pugh Class A and B), reduce initial Cabometyx dose to 40 mg orally once daily and reduce initial Cometriq dose to 80 mg orally once daily. Severe impairment (Child-Pugh Class C): Use is not recommended (has not been studied)	Clinical trials with cabozantinib did not include sufficient numbers of patients aged ≥65 years to determine if efficacy and safety differences exist between older and younger patients	Polypharmacy: If concurrent use of strong CYP3A4 inducers is given with Cabometyx, increase the daily dose by 20 mg; if concurrent use with strong CYP3A4 inhibitor, reduce the daily dose by 20 mg. If concurrent use of strong CYP3A4 inducers are given with Cometriq, increase the daily dose by 40 mg; if concurrent use with strong CYP3A4 inhibitor, reduce the daily dose 40 mg
Pazopanib [69]	No adjustment required for pre-existing mild-severe renal impairment (has not been studied)	No adjustment necessary for mild impairment (bilirubin ≤1.5 times ULN or alanine aminotransferase [ALT] > ULN). Moderate impairment (bilirubin >1.5 to 3 times ULN): consider alternative therapy or reduce to 200 mg once daily	In clinical trials with pazopanib, 199 patients (33%) were aged ≥65 years, and 34 (6%) were aged ≥75 years. No overall differences in efficacy or safety were noted between younger and older patients however, patients >60 years may be at greater risk for liver function abnormalities	Polypharmacy: Avoid concomitant administration with strong CYP3A4 inhibitors and inducers
Regorafenib [70]	No adjustment required for pre-existing mild-severe renal impairment (has not been studied)	No adjustment necessary for pre-existing mild or moderate impairment. Use in severe	In clinical trials with regorafenib, 39% of patients were aged ≥65 and 8% were aged ≥75 years. No overall differences	Polypharmacy: Avoid concomitant administration with strong CYP3A4 inhibitors and inducers

(*continued on next page*)

Table 1 (*continued*)

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
		impairment is not recommended (has not been studied)	in efficacy or safety were noted between younger and older patients	Nutrition: Administer medication with a low-fat meal
Sorafenib [71–72]	Mild impairment (CrCl 40 to 59 mL/min): 400 mg twice daily; moderate impairment (CrCl 20 to 39 mL/min): 200 mg twice daily; severe impairment (CrCl <20 mL/min): not studied. Hemodialysis: 200 mg once daily	Mild impairment (bilirubin >1 to ≤1.5 times ULN and/or AST > ULN): 400 mg twice daily. Moderate impairment (bilirubin >1.5 to ≤3 times ULN; any AST): 200 mg twice daily. Severe impairment (albumin <2.5 g/dL, any bilirubin, any AST): 200 mg once daily or bilirubin >3 to 10 x ULN (any AST): not studied	In clinical trials with sorafenib, 59% of patients were ≥ 65 and 19% were ≥ 75 years. No difference in efficacy or safety was noted between younger and older patients Eisen et al. conducted a retrospective subgroup analysis of data from a large global trial and approximately 59% of patients were aged ≥65 and 19% were ≥ 75 years old. Older patients had a higher incidence of gastrointestinal symptoms and overall higher occurrence of grade 3 adverse events such as anorexia and fatigue	Polypharmacy: Avoid concomitant administration with strong CYP3A4 inhibitors and inducers Nutrition: Take medication on an empty stomach
Sunitinib [73–74]	No adjustment required for pre-existing mild-severe renal impairment. Patients with end-stage renal disease on hemodialysis may require subsequent increased doses due to reduced concentrations	No adjustment necessary for pre-existing mild-to-moderate impairment (Child-Pugh class A or B) and not studied in patients with severe impairment (Child-Pugh Class C)	In clinical trials with sunitinib, 34% of gastrointestinal stromal tumor (GIST) and 27% of primitive neuroectodermal (pNET) patients were aged ≥65 years. No difference in efficacy or safety was noted between younger and older patients Hutson et al. evaluated data from 6 trials examining sunitinib outcomes as a function of age in renal cell carcinoma (RCC). Some adverse events were less common in younger versus older adults, fatigue (60% vs 69%), peripheral edema (17% vs 27%), anemia (18% vs 25%), and thrombocytopenia (16% vs 25%; all $P < .05$)	Polypharmacy: Avoid concomitant administration with strong CYP3A4 inhibitors and inducers. If concomitant administration is warranted, consider a dose reduction with CYP3A4 inhibitors to a minimum of 37.5 mg/day (GIST, RCC) or 25 mg/day (pNET) and consider a dose increase with CYP3A4 inducers to 87.5 mg/day (GIST, RCC) or 62.5 mg/day (pNET).

variations in physiological or homeostatic mechanisms and changes in functional reserves [12]. Older adults have impaired homeostatic mechanisms along with reduced physiology reserves involving all organ systems, and these changes influence their capacity to tolerate treatment and increases the risk of treatment toxicities (e.g., reduced bone marrow reserve is associated with an increased risk for chemotherapy-induced myelosuppression).

Pharmacodynamic changes traditionally have been more difficult to define than pharmacokinetic changes since altered metabolism and/or drug elimination often leads to increased drug concentrations, conflating and intensifying therapy-related adverse effects. For example, older people have increased sensitivity to the cardiovascular effects of anthracyclines (e.g., doxorubicin), which increases the risk for cardiomyopathy [26]. Additionally, age-related changes in oncogenic pathways, the immune system and the tumor microenvironment may also have an impact on the efficacy of drugs that target these systems [27].

Tables 1–5 provide a detailed summary of how age-related pharmacokinetic and physiologic changes affect cancer therapies and include recommendations for dosage adjustments [28–174]. To gather the studies included in this summary, we compiled data from the package insert (e.g., the section with prescribing information for the geriatric population) and from literature searches used to identify published studies that provided information on the use of oncology agents in the older adult population (e.g., pharmacokinetic/pharmacodynamic studies, clinical trials, geriatric assessment invention studies as a predictor of toxicity).

In addition to organ-related dosage modifications, Tables 1–5 also provide specific information on trial data, including efficacy outcomes and adverse drug events based on chronologic age (e.g., age <65 years, ≥65 years, ≥75 years) in order to identify differences between groups. Existing evidence highlights that there are too few older adults included in clinical trials to make evidence-based recommendations on the overall risk versus benefit, but what little is in the literature to date contributes to the (slow) growing body of evidence demonstrating a need for more robust and detailed representation of older adults in clinical trials. Intuitively, it makes sense that older adults with cancer will inherently be at an increased risk for treatment-related toxicity. It is important to note that aside from toxicity concerns, variability in treatment practices can result in mortality differences between older adults compared to younger patients, which is attributed to undertreatment. For example, despite recommendations and documented benefit of chemotherapy for colon cancer, older adults often receive different chemotherapy than younger patients [175–176]. In an analysis of patients with stage III colon cancer, age and co-morbidities are the biggest determinants of whether physicians offer adjuvant chemotherapy [177]. It is critical to emphasize that chronologic age alone is a poor predictor of treatment outcomes because it is not equivalent to functional age. Thus, Tables 1–5 provides information on considerations for oncology agents based on select geriatric assessment (GA) domains.

3. Geriatric Assessment Domains and Influence on Oncology Pharmacology

Using a GA to evaluate patients beyond chronologic age and/or age-related physiologic organ impairment provides a complementary and robust characterization of an older adult's fitness for cancer therapy [178]. The National Comprehensive Cancer Network (NCCN) and the International Society of Geriatric Oncology (SIOG) organizations have developed guidelines that recommend performing a geriatric assessment as part of the initial screening and/or workup for older adults with cancer [7–8]. According to SIOG, the essential domains of the GA include functional status, cognition, comorbidity, geriatric syndromes/mental health status, nutrition, fatigue, polypharmacy and socioeconomic status [8].

Table 2
Summary of monoclonal antibody therapies used in older adults with cancer.

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
Ado-trastuzumab emtansine [75]	No adjustment required pre-existing mild to moderate renal dysfunction. Has not been studied in severe renal dysfunction (CrCl <30 mL/min)	No adjustment required for pre-existing mild to moderate hepatic impairment. Has not been studied in severe hepatic impairment	Of 495 patients who were randomized to ado-trastuzumab in clinical trials, 65 patients (13%) were aged ≥65 age and 11 (2%) were aged ≥75 years. In patients ≥65 years old ($n = 138$ across both treatment arms) the hazard ratios for progression-free survival and overall survival were 1.06 (95% CI: 0.68, 1.66) and 1.05 (95% CI: 0.58, 1.91), respectively. No difference in efficacy or safety was noted between younger and older patients	Comorbidities: Caution should be used in patients with existing cardiovascular disease and/or risk factors for cardiomyopathy Polypharmacy: Avoid concomitant use with strong CYP3A4 inhibitors
Bevacizumab [76]	No adjustment required pre-existing mild to moderate renal dysfunction. Has not been studied in severe renal dysfunction (CrCl <30 mL/min)	No adjustment required for pre-existing mild to moderate hepatic impairment. Has not been studied in severe hepatic impairment	Of the 742 patients enrolled in clinical studies in which all adverse events were captured, 212 (29%) were aged ≥65 and 43 (6%) were aged ≥75 years. Adverse events of any severity that occurred at a higher incidence in the elderly as compared to younger patients were nausea/emesis, ileus, fatigue, gastrointestinal hemorrhage, edema, epistaxis, increased cough, and voice alteration. In an exploratory, pooled analysis of 1745 patients treated in five randomized, controlled studies, there were 618 (35%) patients aged ≥65 years and 1127 patients <65 years. Arterial thromboembolic events occurred more frequently in patients aged ≥65 years	Comorbidities: Caution should be used in patients with existing thrombotic conditions and/or risk factors for cardiovascular events
Blinatumomab [77]	No adjustment required pre-existing mild to moderate renal dysfunction Has not been studied in severe renal dysfunction (CrCl <30 mL/min)	No adjustment required for pre-existing mild to moderate hepatic impairment. Has not been studied in severe hepatic impairment	In clinical trials with blinatumomab, approximately 12% were aged ≥65 and 3% were ≥ 75 years. No overall differences in safety or effectiveness were observed between younger and older patients however, elderly patients experienced a higher rate of neurological toxicities, including cognitive disorder, encephalopathy, confusion, and serious infection	Comorbidities: Caution should be used in patients with existing cognitive impairment and/or risk factors for neurologic events Cytokine release may suppress CYP450 enzymes during initiation of therapy, and impact concomitant drug therapy
Brentuximab vedotin [78]	No adjustment required pre-existing mild to moderate renal dysfunction. Avoid use in patients with CrCl <30 mL/min (has not been studied) The drug conjugate monomethyl auristatin E is excreted renally and toxicities may increase with mild or moderate renal impairment	Reduce initial dose to 1.2 mg/kg (max 120 mg) every 3 weeks for mild hepatic impairment (Child-Pugh A). Avoid in moderate to severe hepatic impairment (Child-Pugh B or C)	Clinical trials did not include sufficient numbers of patients aged ≥65 years to determine whether they respond differently from younger patients. Safety and efficacy have not been fully established	Comorbidities: Caution should be used in patients with existing hepatic and/or renal impairment due to increased risk of toxicity Polypharmacy: Concomitant use with strong CYP3A inhibitors or inducers or P-glycoprotein inhibitors may affect exposure to the monomethyl auristatin E
Cetuximab [79]	No adjustment required pre-existing mild to severe renal dysfunction (has not been studied)	No adjustment required for pre-existing mild to severe hepatic impairment (Child-Pugh A, B or C since it has not been studied)	Of the 1062 patients who received cetuximab with irinotecan or as monotherapy in five studies of advanced colorectal cancer, 363 patients were aged ≥65 years. No overall differences in safety or efficacy were observed between younger and older patients. Clinical studies of cetuximab in head and neck cancer did not include sufficient older adults to determine whether differences exist	Comorbidities: Caution should be used in patients with a history of coronary artery disease, heart failure and arrhythmias Nutrition: Electrolyte imbalances (magnesium, potassium) should be corrected prior to initiation and during therapy
Daratumumab [80]	No adjustment required pre-existing mild to severe renal dysfunction (has not been studied)	No adjustment required for pre-existing mild to severe hepatic impairment (Child-Pugh A, B or C, has not been studied)	Of the 156 patients in myeloma trials on the recommended dose, 45% were aged ≥65 and 10% were aged ≥75 years. No overall differences in safety or effectiveness were observed between these patients and younger patients	Comorbidities: Caution should be used in patients with a history of chronic pulmonary disease due to infusion related respiratory reactions
Necitumumab [81]	No adjustment required pre-existing mild to severe renal dysfunction (has not been studied)	No adjustment required for pre-existing mild to severe hepatic impairment (has not been studied)	Of the 545 patients in the necitumumab plus gemcitabine and cisplatin clinical trial and 108 (20%) were aged ≥70 years and over. The exploratory subgroup analysis reported the hazard ratio for overall	Comorbidities: Caution should be used in patients with a history of coronary artery disease, hypertension and COPD due to increased risk for cardiopulmonary arrest Caution should be used in patients

(continued on next page)

Table 2 (*continued*)

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
			survival in patients aged ≥70 years was 1.03 (95% CI: 0.75, 1.42). There was a higher incidence (≥ 3%) of venous thromboembolic events including pulmonary embolism in patients aged ≥70 compared to younger patients	with pre-existing thrombotic conditions due to increased risk of thromboembolic events Nutrition: Electrolyte imbalances (magnesium) should be corrected prior to initiation and during therapy
Panitumumab [82]	No adjustment required pre-existing mild to severe renal dysfunction (has not been studied)	No adjustment required for pre-existing mild to severe hepatic impairment (has not been studied)	Of 229 patients with colon cancer who received panitumumab, 96 (42%) were aged ≥ age 65. The clinical study did not include a sufficient number of older adults to determine whether they respond differently from younger patients, there were no apparent differences in safety and effectiveness between younger and older adults	Comorbidities: Caution should be used in patients with a history of interstitial pneumonitis or pulmonary fibrosis due to increased risk for pulmonary toxicity Nutrition: Electrolyte imbalances (magnesium and calcium) should be corrected prior to initiation and during therapy
Pertuzumab [83]	No adjustment required pre-existing mild to severe renal dysfunction (has not been studied)	No adjustment required for pre-existing mild to severe hepatic impairment (has not been studied)	Of 402 patients with breast cancer who received pertuzumab in a clinical trial, 60 patients (15%) were aged ≥65 and 5 patients (1%) were aged ≥75 years. No overall differences in efficacy and safety of were observed between younger and older patients	Comorbidities: Caution should be used in patients with a history of congestive heart failure and/or risk factors for cardiomyopathy including uncontrolled hypertension, myocardial infarction, arrhythmias
Ofatumumab [84]	No adjustment required pre-existing mild to severe renal dysfunction (has not been studied)	No adjustment required for pre-existing mild to severe hepatic impairment (has not been studied)	The clinical trials with ofatumumab did not include sufficient numbers of patients aged ≥65 years to determine whether differences exist between younger and older patients	Comorbidities: Caution should be used in patients with a history of renal impairment due to increased risk of tumor lysis syndrome
Ramucirumab [85]	No adjustment required pre-existing mild to severe renal dysfunction (has not been studied)	No adjustment required for pre-existing mild to severe hepatic impairment (has not been studied)	Of the 563 patients treated with ramucirumab in clinical trials for gastric cancer, 36% were aged ≥65 and 7% were aged ≥75 years. No overall differences in safety or effectiveness were observed between younger and older patients `Of the 627 patients who received ramucirumab plus docetaxel or docetaxel monotherapy for NSCLC, 237 (38%) were aged ≥65 and 45 (7%) were aged ≥75 years In an exploratory analysis, the hazard ratio for overall survival in younger patients was 0.74 (95% CI: 0.62, 0.87) and was 1.10 (95% CI: 0.89, 1.36) in older adults Of the 529 patients who received ramucirumab plus FOLFIRI or FOLFIRI alone, 209 (40%) were aged ≥65 and 51 (10%) were aged ≥75 years. Overall, no differences in safety or effectiveness were observed between younger and older adults	Comorbidities: Caution should be used in patients with existing thrombotic conditions and/or risk factors for cardiovascular events
Rituximab [86–87]	No adjustment required pre-existing mild to severe renal dysfunction (has not been studied)	No adjustment required for pre-existing mild to severe hepatic impairment (has not been studied)	In clinical trials evaluating patients with diffuse larger B-cell lymphoma (DLBCL), 927 patients received rituximab in combination with chemotherapy. Of these, 396 (43%) were aged ≥65 and 123 (13%) were aged ≥75 or greater. No overall differences in effectiveness were observed between younger and older adults. Cardiac adverse reactions, mostly supraventricular arrhythmias, occurred more frequently among elderly patients. Serious pulmonary adverse reactions were also more common among the elderly, including pneumonia and pneumonitis. Fischer et al. evaluated rituximab combined with fludarabine and cyclophosphamide for chronic lymphocytic leukemia (CLL) and reported no observed benefit from the addition of rituximab among patients 65 years of age or older, although a benefit was shown with the combination in patients <65. The	Comorbidities: Caution should be used in patients with existing arrhythmias, pulmonary disease and low bone marrow reserve

Table 2 (*continued*)

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
			incidence of grade 3/4 adverse reactions (neutropenia febrile neutropenia, anemia, pancytopenia, infection) was higher in patients aged ≥70 years compared to younger patients	
Trastuzumab [88–89]	No adjustment required pre-existing mild to severe renal dysfunction. Has not been studied	No adjustment required for pre-existing mild to severe hepatic impairment. Has not been studied	In clinical trials using trastuzumab for breast cancer, 386 patients were aged ≥65 years (253 in the adjuvant setting and 133 in the metastatic setting). The risk of cardiac dysfunction was increased in older adults as compared to younger patients in the metastatic setting. Existing data is not adequate to determine whether efficacy improvements are different for younger patients compared to older adults. Singh et al. reported that the risk of cardiac dysfunction appears to be increased for individuals aged ≥65 years compared to younger patients. It is unclear if the risk is based on age or existing cardiac function	Comorbidities: Caution should be used in patients with a history of congestive heart failure and/or risk factors for cardiomyopathy including uncontrolled hypertension, myocardial infarction, arrhythmias
Checkpoint inhibitors [27]				
Atezolizumab [91]	No adjustment required for pre-existing mild to severe renal dysfunction (has not been studied)	No adjustment required for pre-existing mild to severe hepatic impairment (has not been studied)	Of the 310 patients with urothelial carcinoma treated with atezolizumab, 59% were aged ≥65 years. No overall differences in safety or efficacy were observed between younger and older adults	Socioeconomic status: Financial toxicity associated with treatment is a significant challenge. Studies exploring the causes and consequences of costs are critical given the fixed income and financial constraints in this population
Avelumab [92]	No adjustment required for pre-existing mild to severe renal dysfunction (has not been studied)	No adjustment required for pre-existing mild to severe hepatic impairment (has not been studied)	Of the 88 patients with metastatic Merkel cell carcinoma (MCC) treated with avelumab, 75% were aged ≥65 years however, clinical studies of in metastatic MCC had fewer than 100 patients aged 65 and over, therefore, a determination cannot be made as to whether older adults respond differently than younger patients	Socioeconomic status: Financial toxicity associated with treatment is a significant challenge. Studies exploring the causes and consequences of costs are critical given the fixed income and financial constraints in this population
Durvalumab [93]	No adjustment required for pre-existing mild to severe renal dysfunction (has not been studied)	No adjustment required for pre-existing mild to severe hepatic impairment (has not been studied)	Of the 182 patients treated with durvalumab, 112 patients were aged ≥65 years and 34 patients were aged ≥75 years. The overall response rate in patients 65 years or older was 15.2% (17/112) and was 11.8% (4/34) in patients 75 years or older. Grade 3/4 adverse reactions occurred in 38% (42/112) of patients 65 years or older and 35% (12/34) of patients ≥75 years	Socioeconomic status: Financial toxicity associated with treatment is a significant challenge. Studies exploring the causes and consequences of costs are critical given the fixed income and financial constraints in this population
Ipilimumab [94]	No adjustment required for pre-existing mild to severe renal dysfunction (has not been studied)	No adjustment required for pre-existing mild to severe hepatic impairment (has not been studied)	Of the 511 patients treated with ipilimumab in a clinical trial, 28% were aged ≥65 years. No overall differences in safety or efficacy were reported between younger patients and older adult	Socioeconomic status: Financial toxicity associated with treatment is a significant challenge. Studies exploring the causes and consequences of costs are critical given the fixed income and financial constraints in this population
Nivolumab [95]	No adjustment required for pre-existing mild to severe renal dysfunction (has not been studied)	No adjustment required for pre-existing mild to severe hepatic impairment (has not been studied)	Of the 272 patients randomized to nivolumab in a clinical trial, 35% of patients were aged ≥65 years and 15% were aged ≥75 years. Clinical studies did not include sufficient numbers of patients to determine if differences exist between older and younger patients	Socioeconomic status: Financial toxicity associated with treatment is a significant challenge. Studies exploring the causes and consequences of costs are critical given the fixed income and financial constraints in this population
Pembrolizumab [96]	No adjustment required for pre-existing mild to severe renal dysfunction. In a pharmacokinetic study, no difference in clearance was noted for patients with eGFR ≥15 mL/min/1.73 m^2	No adjustment required for pre-existing mild to severe hepatic impairment (has not been studied)	Of 3991 patients with melanoma, NSCLC, head/neck cancer, lymphoma or urothelial cancer who were treated with pembrolizumab in clinical studies, 46% were aged ≥65 years and 16% were aged ≥75 years. No overall differences in safety or effectiveness were observed between younger patients and older adults	Socioeconomic status: Financial toxicity associated with treatment is a significant challenge. Studies exploring the causes and consequences of costs are critical given the fixed income and financial constraints in this population

Table 3
Summary of hormonal therapies used in older adults with cancer.

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
Aromatase inhibitors				
Anastrozole [97–98]	No adjustment required for mild to severe renal impairment	No adjustment required for pre-existing mild to severe hepatic impairment. Has not been studied	In the ATAC study, 45% of patients were aged ≥65 years. The efficacy of anastrozole compared to tamoxifen in patients who were aged ≥65 years (n = 1413 for anastrozole and n = 1410 for tamoxifen, the hazard ratio for disease-free survival was 0.93 [95% CI: 0.80, 1.08) was less than efficacy observed in patients who were <65 years of age (n = 1712 for anastrozole and n = 1706 for tamoxifen, the hazard ratio for disease-free survival was 0.79 [95% CI: 0.67, 0.94). Other clinical trials observed that response rates and time to progression were similar for patients aged ≥65 compared to younger patients	Comorbidities: Caution should be used in patients with a history of reduced bone mineral density, osteopenia and/or existing osteoporosis given the increased risk of toxicities Caution should be used in patients with a history of cardiovascular disease and/or risk factors for cardiovascular events (e.g., myocardial infarction)
Selective estrogen receptor modulators				
Tamoxifen [98, 100]	No adjustment required for mild to severe renal impairment. No adjustment required for ESRD	No adjustment required for pre-existing mild to severe hepatic impairment (Child-Pugh Class A, B, C, has not been studied)	Data shows that older patients with small (<1 cm), node-negative tumors, multiple comorbidities with an estimated survival <10 years are unlikely to derive any survival benefit from tamoxifen Older patients aged ≥65 years had an increased risk of endometrial carcinoma, stroke, deep venous thrombosis, pulmonary embolus, and cataracts. Older adults may experience improved serum lipid profile and preserved bone health versus aromatase inhibitors	Comorbidities: Caution should be used in patients with a history of cardiovascular disease, history of thromboembolic events, and/or risk factors for cardiovascular and/or thrombotic events Polypharmacy: Avoid concurrent use with select selective serotonin reuptake inhibitors that are strong CYP2D6 inhibitors (e.g., fluoxetine, paroxetine) or moderate CYP2D6 inhibitors due to interference with tamoxifen metabolism
Antiandrogens				
Abiraterone [101–102]	No adjustment required for mild to severe renal impairment. No adjustment required for ESRD	No adjustment required for mild hepatic impairment. Reduce dose to 250 mg once daily in patients with moderate hepatic impairment (Child Pugh Class B). Avoid use in severe hepatic impairment (Child-Pugh Class C)	Of the total number of patients receiving abiraterone in phase 3 trials, 73% were aged ≥65 years and 30% were aged ≥75 years. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients	Comorbidities: Caution should be used in patients with a history of cardiovascular disease, specifically heart failure, myocardial infarction and/or arrhythmias due to increased risk of toxicity Polypharmacy: Avoid concurrent use with strong CYP3A4 inducers. If concomitant administration is necessary, increase abiraterone frequency to 1000 mg twice daily
Bicalutamide [102–103]	No adjustment required for mild to severe renal impairment.	No adjustment required for pre-existing hepatic impairment (Child-Pugh Class A, B, C)	No difference in efficacy was noted between younger and older age groups. Older patients aged ≥65 years had an increased risk for cardiovascular mortality (5.5%) when treated with androgen deprivation therapy compared to <65 years old (3.6%)	Comorbidities: Caution should be used in patients with a history of cardiovascular disease, specifically heart failure, myocardial infarction and/or arrhythmias due to increased cardiac risks Caution should be used in patients with a history of reduced bone mineral density, and/or existing osteoporosis because prolonged use is associated increased risk of osteoporosis and fracture Polypharmacy: Avoid concomitant use with QTc-prolonging agents, if possible Avoid concomitant use of strong CYP3A4 inhibitors or strong inducers Nutrition: Bicalutamide is 99% albumin-bound so reduced albumin may lead to increased drug exposure
Enzalutamide [104]	No adjustment required for mild to severe renal impairment (has not been studied)	No adjustment required for pre-existing hepatic impairment (Child-Pugh Class A, B, C)	Of 1671 patients who received enzalutamide in clinical trials, 75% were aged ≥65 years and 31% were aged ≥75. No overall differences in safety or effectiveness were observed between younger and older patients In the AFFIRM trial, patients aged ≥65 years experienced an increased rate of adverse effects including peripheral edema (22.1% vs 12.5%) fatigue (39.7% vs 31.6%) and diarrhea (26.6% vs 19.6%)	Comorbidities: Caution should be used in patients with a history of seizures, cerebrovascular ischemic attacks, Alzheimer disease and/or risk factors for neurologic disorders due to increased risk of toxicity Caution should be used in patients with a history of cardiovascular disease, specifically heart failure, myocardial infarction and/or arrhythmias due to increased risk for cardiovascular disease `Polypharmacy: Avoid concurrent use with strong CYP2C8 inhibitors. If

Table 3 (*continued*)

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
				concomitant administration is necessary, reduce enzalutamide to 80 mg once daily. Avoid concomitant use with strong CYP3A4 inducers. If co-administration is necessary, increase enzalutamide to 240 mg once daily
Gonadotropin-releasing hormone (GnRH) analogues				
Degarelix [103, 105]	No adjustment required for mild to severe renal impairment. Use with caution in severe renal impairment (has not been studied)	No adjustment required for mild-moderate pre-existing hepatic impairment (Child-Pugh Class A, B). Not studied in severe hepatic impairment (Child-Pugh Class C)	Of the total number of subjects in clinical studies of degarelix, 82% were aged ≥65 and 42% were aged ≥75 years. No overall differences in safety or effectiveness were observed between younger patients compared to older adults	Comorbidities: Caution should be used in patients with a history of cardiovascular disease, specifically heart failure, myocardial infarction and/or arrhythmias due to increased cardiac risks `Caution should be used in patients with a history of reduced bone mineral density, and/or existing osteoporosis because prolonged use is associated increased risk of osteoporosis and fracture Polypharmacy: Avoid concomitant use with QTc-prolonging agents, if possible

3.1. Select Domains of the Geriatric Assessment

The GA incorporates cognition assessments using validated screening tools (e.g., Mini-Cog, confusion assessment method) to assess for cognitive impairment and/or delirium [7–8]. Cognitive impairment can influence the pharmacology of cancer agents both directly and indirectly. For example, having a lower baseline cognitive reserve increases the risk for further cognitive decline with exposure to certain oncology treatments known to affect cognition (e.g., antiandrogen therapy, including enzalutamide, for prostate cancer) [104]. Additionally, cognitive impairment can indirectly affect whether a patient is able to adhere to complex medication directions for self-administration of oral cancer drugs or whether a patient is able to understand complex treatment-related tasks. For instance, cognitive impairment can indirectly affect whether a patient can distinguish when to self-manage side effects versus when to contact emergency services and/or the physician for serious adverse events.

The comorbidity component of the GA utilizes validated screening tools (e.g., cumulative illness rating scale) in order to evaluate the type and severity of each medical condition [179]. Older persons with multi-morbidity and decreased physiologic reserves face increased risks that cancer therapies will exacerbate existing chronic conditions and lead to more adverse outcomes. There are many examples of clinically relevant drug-disease interactions that can impact efficacy and safety outcomes in older patients with cancer. Older patients with diabetic peripheral neuropathy with subsequent exposure to taxane-based regimens or miscellaneous agents, like bortezomib, can experience worsened neuropathy and increased risk for gait disturbances and falls/fractures. For older adults with diabetes mellitus who are exposed to high-dose steroids as part of cancer regimens, anti-emetics and/or infusion-related hypersensitivity reactions can lead to hyperglycemia and uncontrolled diabetes. Older patients with chronic renal insufficiency who are exposed to platinum-based regimens, like cisplatin, can experience further deterioration of kidney function and/or acute kidney injury. Older patients with cardiovascular disease with exposure to anthracyclines and/or targeted therapies, like trastuzumab, can experience worsened heart failure. Older patients with heart failure who are exposed to aggressive hydration requirements with platinum-based regimens can experience further decline of cardiac function. Older patients with respiratory disease who receive a bleomycin-based regimen can experience worsened pulmonary toxicity.

Geriatric syndromes such as depression, falls and frailty are captured by performing a GA with validated screening tools [8]. Geriatric syndromes have been linked to multiple adverse clinical outcomes in older adults, hence these syndromes may also influence oncology pharmacology and treatment tolerance. Exposure to cancer treatments may cause treatment-related fatigue or increase the risk for falls, depression and/or osteoporosis. For example, the use of aromatase inhibitors for hormone positive breast cancer may increase the risk for osteoporosis, falls and/or fractures in the older adult oncology population, especially in patients with a history of falls and/or frailty.

A nutritional assessment is a critical part of the GA since malnutrition is a risk factor for chemotherapy intolerance [180]. Oncology drugs can bind to several blood components, such as albumin. Hypoalbuminemia and other nutritional deficiencies can lead to a higher free fraction of drug and therefore higher potential for toxicity based on altered drug distribution and reduced drug clearance. Aside from drug binding, a number of oral oncology therapies have nutritional instructions. For example, regorafenib, which is used to treat advanced refractory colon cancer, requires administration after a low-fat (<30% fat) meal, so it is critical to evaluate patients' nutritional status to ensure dietary considerations can be adhered to without compromising pharmacologic efficacy and toxicity [70].

Polypharmacy assessments (e.g., the Beers criteria, the Screening Tool of Older Persons' potentially inappropriate Prescriptions [STOPP] criteria) are a vital component of the GA. The Beers criteria and the STOPP criteria are validated polypharmacy screening tools and can be utilized to assess medication use [181–182]. Polypharmacy—which generally means the concurrent use of five or more medications and can include unnecessary medication use, medication underuse, use of potentially inappropriate medications in which treatment risks outweigh benefits, and medications that may potentially interact with other medications and/or disease states—is common in older adults with cancer (ranging from 48% to 84%) [183–188]. Use of complementary and alternative medications among ambulatory older adults with cancer is also common (ranging from 17% to 46%), raising concerns about the potential for drug-herbal interactions that increase toxicity risk with anticancer therapies [189–191].

Polypharmacy has been identified as one of the domains of the GA because of its potential influence on health outcomes, including falls, frailty, hospitalization, postoperative complications and mortality [192]. Polypharmacy can also influence oncology pharmacology

Table 4
Summary of miscellaneous therapies used in older adults with cancer.

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
Arsenic trioxide [106–107]	No adjustment required for pre-existing mild to moderate renal dysfunction (CrCl ≥30 mL/min). Use with caution for severe renal impairment (CrCl <30 mL/min) due to higher exposure to metabolites which may require dosage reduction	No adjustment required for pre-existing mild to moderate hepatic impairment. Patients with severe impairment (Child-Pugh class C) should be monitored closely for toxicity	Clinical trials of arsenic did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Older adults aged ≥65 years had an increased risk for hematologic toxicities including leukocytosis (64%) with 17% progressing to differentiation syndrome and grade 3/4 neutropenia (58%). Most common non-hematologic toxicities observed in patients ≥65 years old included cardiac conduction abnormalities, gastrointestinal disturbances, liver dysfunction and edema	Comorbidities: Caution should be used in patients with a history of pre-existing conditions including arrhythmias, lung, heart, kidney and/or liver dysfunction due to increased risk of hematologic and non-hematologic toxicities
Bortezomib [108–109]	No adjustment required for pre-existing mild to severe renal dysfunction including ESRD. Dialysis may increase drug clearance so administer post dialysis	No adjustment required for mild impairment (bilirubin ≤1 times ULN and AST > ULN or bilirubin >1 to 1.5 times ULN). Reduce the dose to 0.7 mg/m^2 to a maximum of 1 mg/m^2 for moderate to severe hepatic impairment (bilirubin >1.5× UNL)	Of the 669 patients enrolled in the relapsed multiple myeloma study, 245 (37%) were aged ≥65 years. Median time to progression and median duration of response for patients aged ≥65 were longer on bortezomib compared to dexamethasone (5.5 mo versus 4.3 mo, and 8.0 mo versus 4.9 months, respectively). The incidence of Grade 3/4 events was 64%, 78% and 75% for bortezomib patients aged ≤50, 51–64 and ≥ 65 years old, respectively. No overall differences in safety or effectiveness were observed between patients aged ≥65 and younger patients	Comorbidities: Caution should be used in patients with a history of pre-existing conditions including diabetic neuropathy, falls and foot ulcers due to increased risk of peripheral neuropathy Polypharmacy: Avoid concomitant use of strong CYP3A4 inducers and inhibitors
Carfilzomib [110]	No adjustment required for pre-existing mild to severe renal dysfunction including ESRD. Administer post dialysis	Reduce dose by 25% in patients with mild (bilirubin >1.5× ULN) to moderate (bilirubin >1.5-3× ULN). Has not studied conducted in severe hepatic impairment (bilirubin >3× UNL)	In clinical trials, there were no differences in efficacy or safety were noted between young and older patients	Comorbidities: Caution should be used in patients with a history of cardiovascular disease, specifically heart failure, pulmonary edema, and myocardial infarction due to increased risk for cardiac events
Everolimus [111–112]	No adjustment required for pre-existing mild to severe renal impairment	Malignancy indications, for mild impairment (Child-Pugh class A), reduce dose to 7.5 mg daily; if not tolerated, reduce further r to 5 mg daily. For moderate impairment (Child-Pugh class B), reduce dose to 5 mg once daily; if not tolerated, reduce further to 2.5 mg once daily. For severe impairment (Child-Pugh class C), a maximum dose of 2.5 mg once daily may be used	In clinical trials with advanced hormone receptor positive, HER2-negative breast cancer patients, 40% of everolimus treated patients were aged ≥65 and 15% were aged ≥75 years. No overall differences in effectiveness were observed between younger patients and older adults. The incidence of deaths due to any cause within 28 days of the last everolimus dose was 6% in patients aged ≥65 years of age versus 2% in younger patients. Adverse reactions leading to treatment discontinuation occurred in 33% of patients aged ≥65 compared to 17% in younger patients	Comorbidities: Caution should be used in patients with a history of pre-existing conditions including diabetes and/or hyperglycemia, hyperlipidemia and hypertriglyceridemia due to an increased risk of metabolic-related events
			In the randomized advanced renal cell cancer study, 41% of everolimus treated patients were aged ≥65 years and 7% were aged ≥75 years. In the randomized advanced PNET study, 30% of everolimus treated patients were aged ≥65 years and 7% were aged ≥75 years. No overall differences in safety or effectiveness were observed between older and younger patients	Polypharmacy: Avoid use with concomitant strong CYP3A4 and P-glycoprotein inhibitors or inducers. If co-administration is required, specific dose adjustments are required based off specific indication
Ixazomib [113]	No adjustment required for pre-existing mild to moderate renal impairment. Reduce dose to 3 mg for severe impairment (CrCl ≤30 mL/min) including dialysis	No adjustment required for mild hepatic impairment. Reduce to 3 mg weekly for Child Pugh Class B or Class C (bilirubin >1.5× ULN)	Of the total number of subjects in clinical studies of ixazomib, 55% were aged ≥65 and 17% were aged ≥75 years. No overall differences in safety or effectiveness were observed between elderly and younger patients	Polypharmacy: Avoid concomitant administration with CYP3A4 inducers or inhibitors Nutrition: Take medication on an empty stomach. Ixazomib is 99% albumin-bound so reduced albumin may lead to increased drug exposure

Table 4 (*continued*)

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
Lenalidomide [114]	No adjustment required for pre-existing mild renal impairment. Reduce dose for moderate impairment (CrCl 30 to 60 mL/min) to 10 mg daily (lymphoma, myeloma) and 5 mg once daily for MDS. Reduce for severe impairment (CrCl <30 mL/min) to 15 mg every 48 h (lymphoma, myeloma) and 2.5 mg daily for MDS. In dialysis, reduce dose to 5 mg daily (lymphoma, myeloma) and 2.5 mg daily for MDS. Administer post-dialysis on dialysis days	No adjustment required for pre-existing mild to severe hepatic impairment. Has not been studied	Lenalidomide has been used in multiple myeloma trials in patients up to 86 years of age. Of the 703 myeloma patients in two clinical trials, 45% were aged ≥65 and 12% were aged ≥75 years. Patients >65 years were more likely than patients ≤65 years of age to experience DVT, pulmonary embolism, atrial fibrillation, and renal failure following use of lenalidomide. No differences in efficacy were observed between elderly and younger patients Of the 148 patients with MDS enrolled in the major study, 38% were aged ≥65 and 33% were aged ≥75 years. Although the overall frequency of adverse events (100%) was the same in patients over 65 versus younger patients, the frequency of serious adverse events was higher in older adults (54% vs. 33%). A greater proportion of patients aged ≥65 discontinued from studies because of adverse events compared to younger patients (27% vs.16%). No differences in efficacy were observed between patients over 65 years of age and younger patients	Comorbidities: Caution should be used in patients with a history of arrhythmias, thrombotic events and renal failure due to increased risks of adverse effects
Olaparib [115]	No adjustment required for pre-existing mild renal impairment. Reduce dose for moderate impairment (CrCl 31 to 50 mL/min) to 300 mg twice daily. For severe impairment (CrCl ≤3 0 mL/min) or dialysis no dose adjustments provided (has not been studied)	No adjustment required for pre-existing mild to severe hepatic impairment (has not been studied)	In clinical studies with olaparib, 482 patients with advanced solid tumors were included and 135 (28%) patients were aged ≥65 years. There appeared to be no major difference in the safety profile of patients treated with olaparib aged <65 years versus ≥65 years. In clinical studies, patients aged ≥65 years old were at greater risk of grade 3/4 toxicities including anemia, thrombocytopenia, lymphopenia and asthenia compared to younger patients	Polypharmacy: Avoid concomitant use with CYP3A4 inhibitors and CYP3A4 inducers. If co-administration is necessary with moderate CYP3A4 inhibitors adjust the dose to 200 mg twice daily, strong CYP3A4 inhibitors adjust the to 150 mg twice daily
Palbociclib [116]	No adjustment required for pre-existing mild to moderate renal impairment (has not been studied in severe renal impairment)	No dose adjustment for pre-existing mild to severe hepatic impairment (has not been studied)	Of 84 patients who received palbociclib in a clinical study, 37 patients (44%) were aged ≥65 years and 8 patients (10%) were aged ≥75 years. No overall differences in safety or effectiveness of palbociclib were observed between younger patients and older adults	Polypharmacy: Avoid strong CYP3A4 inhibitors. If concomitant use cannot be avoided reduce the dose to 75 mg once daily with food. Avoid concomitant use with strong CYP3A inducers, if possible
Pomalidomide [117]	No adjustment required for pre-existing mild to severe renal impairment (has not been studied). Reduce dose to 3 mg for patients on dialysis. Administer post-dialysis on dialysis days	Reduce dose to 3 mg once daily form mild-moderate hepatic impairment (Child Pugh Class A, B). Reduce dose to 2 mg once daily for severe hepatic impairment (Child Pugh Class C)	Of the total number of patients in clinical studies of pomalidomide, 41% were aged ≥65 and 12% were aged ≥75 years. No overall differences in effectiveness were observed between these patients and younger patients	Comorbidities: Caution should be used in patients with a history of thromboembolic events, myocardial infarction and stroke due to an increased risk for thromboembolic –related adverse events Polypharmacy: Avoid concomitant use of strong CYP1A2 inhibitors. If concomitant use of strong CYP1A2 inhibitors cannot be avoided, reduce pomalidomide by 50%
Rucaparib [118]	No adjustment required for pre-existing mild to severe renal impairment (has not been studied)	No dose adjustment for pre-existing mild to severe hepatic impairment (has not been studied)	One hundred and sixty (42%) of the 377 ovarian cancer patients in clinical trials of rucaparib were aged ≥65 years. No overall differences in safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. The effectiveness of rucaparib in patients with BRCA-mutant ovarian cancer who were 65 years of age or older could not be assessed due to the small number of patients ($N = 38$)	Polypharmacy: Avoid concomitant use of moderate or strong CYP 3A4 inhibitors. If concomitant use is warranted with moderate CYP3A4 inhibitors, decrease the dose to 200 mg twice daily or with strong inhibitors decrease to 150 mg twice daily

(*continued on next page*)

Table 4 (*continued*)

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
Temsirolimus [119–120]	No adjustment required for pre-existing mild to severe renal impairment (has not been studied)	For mild hepatic impairment (bilirubin >1 to 1.5 x ULN or AST > ULN with bilirubin ≤ULN), reduce dose to 15 mg once weekly. For moderate to severe hepatic impairment (bilirubin >1.5 x ULN), use is contraindicated	Clinical studies of temsirolimus did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Patients aged ≥65 years old had an increased incidence of diarrhea, edema and pneumonia Case reports using temsirolimus in older adults (aged ≥65 years) experienced increased incidence of pneumonitis	Polypharmacy: Avoid concomitant CYP 3A4 inducers and inhibitors. If coadministration is required with a CYP3A4 inhibitors decrease 12.5 mg once weekly. If co-administration is required with a CYP3A4 inhibitor increase the dose to 50 mg once weekly
Vismodegib [121–122]	No adjustment required for pre-existing mild to severe renal impairment	No dose adjustment for pre-existing mild to severe hepatic impairment	Clinical studies of vismodegib did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients	Nutrition: Vismodegib is 99% albumin-bound so reduced albumin may lead to increased drug exposure

because it increases the risk for drug interactions that can lead to adverse drug events. In cohorts of older adults with cancer, drug interaction rates have been as high as 75% [18–20, 193]; specific examples of these interactions have been detailed above. Aside from drug interactions, medication adherence has also become increasingly important in the setting of polypharmacy, especially given the accelerated expansion and development of oral chemotherapy. A systematic review of determinants that influence adherence to oral chemotherapy drugs showed that older age was a factor [194]. Assessing medication adherence in the older adult population can be challenging given the variable methods that exist for measuring and improving medication adherence [195–196].

Lastly, socioeconomic support is an integral part of the GA because social isolation has been linked to increased chemotherapy toxicity [180]. Older adults are often challenged in terms of financial resources, health literacy and access to healthcare, all of which may influence oncology pharmacology and treatment tolerance [7]. For example, having access to reliable caregiver support can impact an older adult's ability to make informed treatment decisions, make provider appointments, show up for outpatient treatments and/or laboratory tests, to manage complex oral chemotherapy regimens (e.g., take twice daily with food for 14 days out of 21 days) and/or to seek medical attention when adverse treatment-related effects occur. Additionally, the high cost or financial toxicities associated with many of the novel oncology drugs, such as checkpoint inhibitor immunotherapies, should be considered given the fixed income and financial constraints that are common in this population [90].

4. Chemotherapy Toxicity Risk Predictive Tools and Influence on Oncology Pharmacology

Chemotherapy predictive tools integrating both patient-related characteristics captured in the GA and physiological factors can help clinicians predict chemotherapy toxicity risk. Such tools capture the prevalence of chemotherapy-related toxicity as grade three (hospitalization), grade four (life threatening adverse event), and grade five (treatment-related death). The Cancer and Aging Research Group developed a validated predictive model from the results of a pre-chemotherapy survey of 500 older adults; the eleven-question survey collected information on patient age, number of chemotherapy drugs, chemotherapy dosing, and laboratory values and variables from the geriatric assessment [180, 197]. The tool identified risk factors for chemotherapy-related toxicity and combined them to develop a predictive model for which patients are at risk. The tool identified an estimated risk of chemotherapy toxicity ranging from 25% (lowest risk group) to 89% (highest risk group) [180].

Extermann and colleagues developed the Chemotherapy Risk Assessment Scale for High-Age Patients, a predictive model for determining severe chemotherapy toxicity in older adults [198]. This instrument was based on a study evaluating 518 older patients (≥70 years) prior to initiation of a new cancer regimen. The study was designed to predict grade three or greater non-hematologic toxicity and grade four or greater hematologic toxicity. The tool identified an estimated risk for non-hematologic toxicity ranging from 33% (lowest risk group) to 93% (highest risk group) and the estimated risk for hematologic toxicity ranged from 7% (lowest risk group) to 100% (highest risk group).

Both tools are user-friendly and have helped to establish the practice of global risk assessment toxicity in an older adult population [180, 197–198]. Some notable limitations exist with both tools, since many of the chemotherapy regimens prescribed in these studies were limited to single- and multi-agent, conventional chemotherapy regimens; since the studies did not include high-dose chemotherapy, monoclonal antibodies (e.g., pertuzumab), immunotherapies (e.g., nivolumab), or novel oral treatments (e.g., palbociclib), results may not transfer over to populations receiving these treatments. Furthermore, both predictive models focused on grade three or higher toxicity, but grade two toxicity may be equally important in this older population given how comorbidities and functional status can influence patient outcomes [197].

5. Future Directions

Despite the well-documented link between cancer and age-related physiologic changes, there is a lack of robust data to support clinicians in making evidence-based decisions regarding treatment with cancer therapies in older adults, especially those over age 75. Some studies reporting conflicting results on the age-related physiologic changes of cancer therapies agents may be limited by small sample sizes that restrict detection of age-related differences. Emerging studies draw attention to the fact that several factors beyond age can affect an older adult's ability to tolerate cancer therapy. Broadening clinical oncology trials to capture not only chronological age but also domains within the GA would allow clinicians to better identify which characteristics and subsets of older adults who may benefit from treatment and versus others who are most vulnerable to morbidity and/or mortality. Existing gaps create an urgent need for future research studies to include a robust and detailed characterization of how GA domains including cognition, comorbidity, functional status, geriatric syndromes, nutrition, polypharmacy and socioeconomic can influence the pharmacology of cancer therapies.

Table 5
Summary of traditional cancer therapies used in older adults with cancer.

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
Alkylating agents				
Bendamustine [123–124]	No adjustment required for pre-existing mild to severe renal impairment	No adjustment required for pre-existing mild hepatic impairment. Avoid in patients with moderate (AST 2.5 to 10 x ULN and total bilirubin 1.5 to 3 x ULN) or severe (total bilirubin >3 x ULN) hepatic impairment (has not been studied)	In clinical CLL trials with bendamustine, 153 patients received bendamustine. The overall response rate for patients younger than 65 years of age was 70% ($n = 82$) for bendamustine hydrochloride and 30% ($n = 69$) for chlorambucil. The overall response rate for patients aged ≥65 years was 47% ($n = 71$) for bendamustine and 22% ($n = 79$) for chlorambucil. In patients younger than 65 years of age, the median progression-free survival was 19 months in the bendamustine group and 8 months in the chlorambucil group. In patients 65 years or older, the median progression-free survival was 12 months in the bendamustine group and 8 months in the chlorambucil group. In lymphoma trials, overall response rate and duration of response was similar in patients <65 years and patients aged ≥65 years. There were no clinically significant differences in the adverse reaction profile between younger patients and older adults Laurenti et al. retrospectively evaluated bendamustine combined with rituximab as first-line therapy in patients aged ≥65 years. Efficacy was established in this cohort with the exception of patients with deletion 17. Dose reductions (70 mg/m^2) were required in >50% of patients. Grade 3/4 hematologic toxicity, most commonly neutropenia, occurred in 37.1% of patients. Grade 3/4 non-hematologic toxicity included pneumonia and infusion reactions, occurred in 25.7% of patients	Comorbidities: Caution should be used in patients with compromised bone marrow reserve due to increased risk of hematologic toxicity Polypharmacy: Avoid concomitant use with CYP1A2 inducers or inhibitors
Busulfan [125]	No adjustment required for pre-existing mild to severe renal impairment (has not been studied)	No adjustment for pre-existing mild to severe hepatic impairment (has not been studied)	In a transplant clinical trial, 5 out of 61 patients treated with intravenous busulfan as a conditioning regimen for transplant were over the age of 55 (range 57–64). Each of these patients achieved myeloablation and engraftment	Polypharmacy: Acetaminophen may decrease the clearance of busulfan. Avoid acetaminophen within 72 h of co-administration, if possible
Carboplatin [126–127]	Dose determination with Calvert formula uses glomerular filtration rate and adjusts for renal dysfunction	No adjustment for pre-existing mild to severe hepatic impairment	In the initial combination therapy studies, 395 out of 789 patients were treated with carboplatin with cyclophosphamide. Of these, 141 patients were aged ≥65 years and 22 were aged ≥75 years. Age was not a prognostic factor for survival. Older adults were more likely to have severe thrombocytopenia compared to younger patients. In a combined database of 1942 patients (414 were aged ≥65 years) and received single agent carboplatin for multiple tumor types. A similar incidence of adverse events was seen in patients aged ≥65 years compared to younger patients Ramalingam et al. evaluated the use of carboplatin combined with paclitaxel in 136 patients aged ≥70 years with NSCLC. Grade 3/4 anemia was more common in weekly dosing compared to every 3 weeks (16% vs. 6%), while neuropathy was seen less	Comorbidities: Caution should be used in patients with compromised bone marrow reserve due to increased risk of hematologic toxicity Caution should be used in patients with preexisting renal impairment due to the increased risk hematologic and non-hematologic toxicities Polypharmacy: Minimize exposure to concurrent nephrotoxic medications

(continued on next page)

Table 5 (*continued*)

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
			frequently with a weekly schedule	
Cisplatin [128–132]	Do not administer a repeat course until the serum creatinine is below 1.5 mg/dL, and/or the BUN is below 25 mg/dL Aronoff et al. proposed dosing recommendations for patients with pre-existing renal impairment: Reduce dose by 25% for moderate-severe renal impairment (CrCl 10–50 mL/min), reduce dose by 50% for severe renal impairment (CrCl <10 mL/min). Cisplatin is partially dialyzed, administer 50% of dose post-hemodialysis	No adjustment for pre-existing mild to severe hepatic impairment (has not been studied)	In four clinical trials, 426 out of 1484 patients (29%) were aged ≥65 years with advanced ovarian carcinoma and received cisplatin combined with cyclophosphamide or paclitaxel. Age was not found to be a prognostic factor for survival. A secondary analysis showed that elderly patients had a shorter survival vs. younger patients In some of these trials, elderly patients had a higher incidence of severe neutropenia, thrombocytopenia, and leukopenia compared to younger patients. In two trials where non-hematologic toxicity was evaluated according to age, elderly patients had a higher incidence of peripheral neuropathy, infectious complications, and nephrotoxicity	Comorbidities: Caution should be used in patients with compromised bone marrow reserve due to increased risk of hematologic toxicity Caution should be used in patients with preexisting renal impairment due to the increased risk of nephrotoxicity and other hematologic and non-hematologic toxicities Caution should be used in patients with a history of heart failure due to increased risk of worsening heart failure associated with aggressive pre- and post-hydration requirements with cisplatin Polypharmacy: Minimize exposure to concurrent nephrotoxic medications
Cyclophosphamide [133–135]	No adjustment required for pre-existing mild to severe renal impairment based on the package insert. Aronoff et al. proposed recommendations for patients with pre-existing renal impairment - no adjustment required for pre-existing mild renal impairment. Consider dosage reduction in patients with moderate to severe renal impairment. In hemodialysis, 20%–50% is dialyzed, administer dose after hemodialysis	No adjustment for pre-existing mild to severe hepatic impairment based on the package insert. Floyd et al. proposed recommendations for patients with pre-existing hepatic impairment. Reduce the dose by 25% for mild to moderate hepatic impairment (serum bilirubin 3.1 to 5 mg/dL or transaminases >3× ULN). Avoid use in severe hepatic impairment (serum bilirubin >5 mg/dL)	No difference in safety and efficacy was noted between young and older patients yet, insufficient data from clinical studies exist to determine if differences exist Wildiers et al. reported that no pharmacokinetic differences exist based on age, although differences in safety (pharmacodynamic differences) were noted including with increased myelosuppression	Comorbidities: Caution should be used in patients with compromised bone marrow reserve due to increased risk of hematologic toxicity Caution should be used in patients receiving high doses of cyclophosphamide with advanced age, a history of cardiovascular disease due to increased risk for cardiotoxicity Polypharmacy: Minimize exposure to concomitant treatment with other cardiotoxic agents to reduce the risk of cardiotoxicity associated with high doses of cyclophosphamide
Ifosfamide [132, 134, 136–137]	No adjustment required for pre-existing mild to severe renal impairment based on the package insert. Aronoff et al. proposed recommendations for patients with pre-existing renal impairment - no adjustment required for pre-existing mild to severe renal impairment. Reduce dose by 25% for severe renal impairment (CrCl <10 mL/min)	No adjustment for pre-existing mild to severe hepatic impairment based on the package insert. Floyd et al. proposed recommendations for patients with pre-existing hepatic impairment. For mild hepatic impairment, reduce dose by 75% for moderate to severe hepatic impairment (serum bilirubin >3 mg/dL)	No difference in safety and efficacy was noted between young and older patients yet, insufficient data from clinical studies exist to determine if differences exist De Pas et al. suggested dose modification in elderly patients should be considered, based on increased volume of distribution, lower serum albumin, and higher serum creatinine, although no they provided no evidence based guidelines	Comorbidities: Caution should be used in patients with pre-existing renal impairment due to the increased risk of toxicity Caution should be used in patients with a history of heart failure due to increased risk of fluid overload with hydration Caution should be used in patients with a history of neurotoxicity due to increased risk of central nervous system toxicity Polypharmacy: Minimize exposure to concomitant treatment with CYP3A4 inhibitors and inducers
Oxaliplatin [138–140]	No adjustment required for pre-existing mild to moderate renal impairment (CrCl ≥30 mL/min). Reduce to 65 mg/m^2 for severe renal impairment (CrCl <30 mL/min)	No adjustment for pre-existing mild to severe hepatic impairment	In clinical trials with adjuvant oxaliplatin for colon cancer, 400 patients were aged ≥65 years. Efficacy in patients aged ≥65 years was inconclusive. Patients aged ≥65 years experienced a higher incidence of grade 3/4 granulocytopenia compared to younger patients (45% versus 39%) In advanced colon cancer, similar efficacy was observed in patients aged ≥65 years compared to the overall study population. The rates of grade 3/4 toxicity were similar across age groups although diarrhea, dehydration, hypokalemia, leukopenia, fatigue, and syncope were higher in older adults. Dose limiting toxicities include neuropathy and myelosuppression. Conflicting information describes whether age influences development of oxaliplatin induced neuropathy	Comorbidities: Caution should be used in patients with compromised bone marrow reserve due to increased risk of hematologic toxicity Caution should be used in patients with a history of pre-existing conditions including peripheral neuropathy, falls due to increased risk for neuropathy

Table 5 (*continued*)

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
Antimetabolites				
Capecitabine [141–144]	No adjustment required for pre-existing mild renal impairment (CrCl ≥51 mL/min). Reduce dose by 25% for moderate renal impairment (CrCl 30–50 mL/min). Use is contraindicated with severe renal impairment (CrCl <30 mL/min)	No adjustment required for pre-existing mild to moderate hepatic impairment. No adjustments noted for severe hepatic impairment (has not been studied)	Patients aged ≥80 years may experience a greater incidence of grade 3/4 adverse reactions. In 875 patients with metastatic breast or colorectal cancer who received capecitabine monotherapy, 62% of the 21 patients aged ≥80 years experienced a treatment-related grade 3/4 adverse event including diarrhea in 6 (28.6%), nausea in 3 (14.3%), hand-foot syndrome in 3 (14.3%), and vomiting in 2 (9.5%) patients. Among the 10 patients aged ≥70 years treated with capecitabine with docetaxel, 30% (3 out of 10) experienced grade 3/4 diarrhea and stomatitis, and 40% (4 of 10) experienced grade 3 hand-foot syndrome In 995 patients receiving capecitabine as adjuvant therapy for colon cancer, 41% of the 398 patients were aged ≥65 years experienced a treatment-related grade 3/4 adverse event including hand-foot syndrome in 75 (18.8%), diarrhea in 52 (13.1%), stomatitis in 12 (3.0%), neutropenia/granulocytopenia in 11 (2.8%), vomiting in 6 (1.5%), and nausea in 5 (1.3%) patients Other studies and reports have been conducted which suggests that capecitabine is effective and well tolerated in elderly patients. Bajetta et al. suggests that a reduced dose of 1000 mg/m^2 twice daily merits consideration as "standard" for older patients who do not have severely impaired renal function	Comorbidities: Caution should be used in patients with a history of coronary artery disease myocardial infarction, ischemia, arrhythmias, angina and cardiac failure due to increased risk of cardiotoxicity Caution should be used in patients with a history of renal impairment and/or concomitant use of nephrotoxic medications Polypharmacy: Capecitabine may increase the INR and bleeding risk in patients on concomitant coumarin-derived anticoagulants Nutrition: Take medication with food or within 30 min after a meal
Cytarabine [134, 145–146]	No adjustment required for pre-existing mild to severe renal impairment. Reduction may be warranted depending on dose. Smith et al. proposed dosing recommendations for patients with pre-existing renal impairment receiving high-dose cytarabine ≥2 g/m^2/dose: Reduce dose to 1 g/m^2/dose for SrCr 1.5–1.9 mg/dL or increase from baseline of 0.5 to 1.2 mg/dL. Reduce dose to 0.1 g/m^2/day as a continuous infusion for SrCr ≥2 mg/dL or increase from baseline of >1.2 mg/dL	No adjustment required for pre-existing mild to severe hepatic impairment. Floyd et al. proposed recommendations for patients with pre-existing hepatic impairment. Reduce dose by 50% for elevated transaminases	Sufficient information is not available to identify differences in efficacy and safety between young patients and older adults (aged ≥65 years). High dose cytarabine was not well tolerated in older adults due to neurotoxicity.	Comorbidities: Caution should be used in patients with a history of neurologic impairment (e.g., seizures) due to increased risk of neurotoxicity associated with high dose treatment Caution should be used in patients with a history of renal impairment and/or concomitant use of nephrotoxic medications
Fluorouracil [132, 134, 147–149]	No adjustment required for pre-existing mild to severe renal impairment. Aronoff et al. proposed recommendations for patients with ESRD on hemodialysis – administer 50% of standard dose following hemodialysis	No adjustment required for pre-existing mild to severe hepatic impairment. Floyd et al. proposed recommendations for patients with pre-existing hepatic impairment – avoid use in severe hepatic impairment (bilirubin >5 mg/dL)	Reported clinical experience has not identified differences in safety or effectiveness between elderly and younger patients Folprecht et al. conducted a retrospective analysis of 3825 patients who received a 5-fluorouracil (5-FU)-containing treatment in 22 European trials and identified 629 patients aged ≥70 years. The study reported an equal overall survival in elderly patients [10.8 months, 95% confidence interval (CI) 9.7–11.8] and in younger patients (11.3 months, 95% CI 10.9–11.7; $P = .31$). Response rate	Comorbidities: Caution should be used in patients with a history of coronary artery disease myocardial infarction, ischemia, arrhythmias, angina and cardiac failure due to increased risk of cardiotoxicity Caution should be used in patients with a history of renal impairment and/or concomitant use of nephrotoxic medications Polypharmacy: Capecitabine may increase the INR and bleeding risk in patients on concomitant coumarin-derived anticoagulants

(*continued on next page*)

Table 5 (*continued*)

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
			did not differ between age groups ≥70 and < 70 years (23.9% and 21.1%; respectively; $P = .14$) Lim et al. conducted a feasibility study to assess a modified fluorouracil-based regimen in elderly patients (≥ 80 years) with metastatic gastric cancer (GC) or colorectal cancer (as first line treatment). Median progression-free survival and overall survival were 5.4 and 6.6 months in the GC group and 7.3 and 8.1 months in the colorectal cancer group, respectively. There was no significant difference in progression free survival ($p = .941$) and OS ($p = .238$) between the GC and the colorectal cancer group. The 1-year survival rates were 35.7% with GC and 42.9% with colorectal cancer. Common grade 3/4 hematology toxicities were neutropenia (10.7%) and anemia (14.3%)	
Methotrexate [132, 134, 150–151]	No adjustment required for pre-existing mild renal impairment based on package insert. Aronoff et al. proposed recommendations for patients with moderate to severe renal impairment (CrCl 10–50 mL/min), administer 50% of standard dose. Avoid use in severe renal impairment (CrCl <10 mL/min). For ESRD on dialysis, administer 50% of the dose post-dialysis	No adjustment required for pre-existing mild to severe hepatic impairment based on package insert. Floyd et al. proposed recommendations for patients with pre-existing hepatic impairment – reduce dose by 25% for moderate to severe hepatic impairment (bilirubin 3.1 to 5 mg/dL or transaminases >3 times ULN. Avoid use in severe hepatic impairment (bilirubin >5 mg/dL)	Reported clinical experience has not identified differences in safety or effectiveness between elderly and younger patients Zhu et al. retrospectively studied the response and adverse effects of high-dose methotrexate (MTX) in patients who were aged ≥70 years. Thirty one patients with primary central nervous system (CNS) lymphoma receiving high-dose methotrexate (3.5–8 g/m^2) as initial therapy from 1992 through 2006. Overall, 87.9% of the cycles required dose reduction because of impaired creatinine clearance. In 30 evaluable patients, progression free survival and overall survival were 7.1 months and 37 months, respectively. Grade 3/4 toxicities were observed in 27 of 31 patients and included gastrointestinal disturbances in 58% (3.2% grade 3), hematological complications in 80.6% (6.5% grade 3), and renal toxicity in 29% (0% grade 3/4). The authors concluded that high-dose MTX is associated with a high proportion of radiographic responses and a low proportion of grade 3/4 toxicity in patients 70 or more years of age with primary CNS lymphoma	Comorbidities: Caution should be used in patients with renal impairment Polypharmacy: Caution should be used in patients with concomitant NSAID therapy due to concern for elevated and prolonged methotrexate levels Caution with concomitant use of nephrotoxic medications due to concern for elevated and prolonged methotrexate levels Caution should be used with methotrexate and concomitant proton pump inhibitors due to concern for elevated and prolonged methotrexate levels and metabolites which may lead to increased toxicity
Pemetrexed [152–154]	No adjustment required for pre-existing mild renal impairment. Use is not recommended for moderate renal impairment (CrCl <45 mL/min) since an insufficient number of patients have been studied for dosage recommendations.	No adjustment required for pre-existing mild to moderate hepatic impairment based on package insert	In the initial NSCLC trial, 37.7% of patients initially treated with pemetrexed plus cisplatin were aged ≥65 years and grade 3/4 neutropenia was greater as compared to patients <65 years (19.9% versus 12.2%). For patients <65 years, the hazard ration (HR) for overall survival was 0.96 (95% CI: 0.83, 1.10) and for patients ≥65 years the HR was 0.88 (95% CI: 0.74, 1.06) Paz-Ares conducted a meta-analysis to examine the impact of age on overall survival in NSCLC patients treated with pemetrexed. Data from 2671 patients spanned four phase 3	Comorbidities: Caution should be used in patients with a history of renal impairment and/or concomitant use of nephrotoxic medications Polypharmacy: Caution should be used in patients with a history of renal impairment and concomitant NSAID use. Avoid NSAIDs with short half-lives (e.g., ibuprofen, ketorolac) for 2 days before, the day of, and for 2 days post pemetrexed. Avoid NSAIDs with long half-lives (e.g., naproxen) for 5 days before, the day of, and 2 post pemetrexed

Table 5 (*continued*)

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
			studies included 32% of patients who were aged ≥65 years and 14% were aged ≥70 years. The pooled ratio of the overall survival HR (pemetrexed versus control) in patients <65 years to that in patients ≥65 years was 0.92 (95% confidence intervals [CI] 0.67–1.25). The effect of pemetrexed on overall survival was not found to be different in younger and older patients undergoing treatment in the first-line, second-line, or maintenance settings Hata et al. conducted a retrospective study to evaluate the efficacy and safety of pemetrexed monotherapy for chemo-naïve elderly patients aged ≥80 with NSCLC. The study reported that single agent pemetrexed demonstrated similar efficacy and safety between aged ≥80 and aged 70–79 populations	
Pralatrexate [155]	No adjustment required for pre-existing mild renal impairment (eGFR ≥30 mL/min/1.73 m^2). Reduce dose to 15 mg/m^2 for moderate to severe renal impairment (eGFR 15 to <30 mL/min/1.73 m^2) Initial: Reduce dose to 15 mg/m^2. Avoid use in ESRD including dialysis	No adjustments for pre-existing hepatic impairment were provided since formal studies have not been performed. Patients with hepatic impairment were excluded from clinical trials	In a peripheral T-cell lymphoma clinical trial, 36% of patients (n = 40) were aged ≥65 years. No overall differences in efficacy and safety were observed in patients based on age (< 65 years compared with ≥65 years)	Comorbidities: Caution should be used in patients with a history of renal impairment and/or concomitant use of nephrotoxic medications Polypharmacy: Caution should be used with pralatexate and concomitant drugs with renal clearance like NSAIDs due to concern for delayed pralatrexate clearance
Anti-microtubule agents				
Cabazitaxel [156]	No adjustment required for pre-existing mild to severe renal impairment	Reduce the starting dose to 20 mg/m^2 in patients with mild hepatic impairment (total bilirubin >1 to ≤ 1.5 x ULN or AST > 1.5 x ULN). Reduce the starting dose to 15 mg/m^2 in patients with moderate hepatic impairment (total bilirubin >1.5 to ≤ 3 x ULN, with any AST). Use is contraindicated in patients with severe hepatic impairment (total bilirubin >3 x ULN)	In clinical trials, 240 of the 371 patients treated with cabazitaxel were aged ≥65 and 70 patients were aged ≥75 years old. No difference was noted in efficacy between older versus younger patients. Death due to causes other than prostate cancer, occurred in 15 (6%) of patients over 65 versus 3 patients (3%) <65 years. Grade 3/4 neutropenia (84% vs. 74%) and febrile neutropenia (8% vs. 6%) occurred more frequently in patients over 65 compared to younger patients. No difference was observed in efficacy between younger patients compared to older adults	Comorbidities: Caution should be used in patients with compromised bone marrow reserve due to increased risk of hematologic toxicity Caution should be used in patients with a history of pre-existing conditions including peripheral neuropathy, falls due to increased risk for neuropathy Caution should be used in patients with a history of pulmonary diseases due to increased risk of pneumonia, pneumonitis Polypharmacy: Minimize exposure to concomitant treatment strong CYP3A4 inhibitors. Decrease the dose of cabazitaxel by 25% if concomitant use is necessary
Eribulin [157–158]	No adjustment required for pre-existing mild renal impairment. Reduce the dose to 1.1 mg/m^2 in patients with moderate to severe renal impairment (CrCl 15–49 mL/min)	Reduce starting dose to 1.1 mg/m^2 in patients with mild hepatic impairment (Child-Pugh A). Reduce dose to 0.7 mg/m^2 for patients with moderate hepatic impairment (Child-Pugh B). No adjustments noted for severe hepatic impairment (Child-Pugh C, has not been studied)	Muss et al. evaluated eribulin in older patients aged ≥60 years with metastatic breast cancer compared to younger patients. Efficacy was similar between all age groups. Overall safety was comparable but grade 3/4 reactions including asthenia or fatigue (13.9% vs. 5.9%) and peripheral neuropathy (10.1% vs. 4.0%) occurred more frequently in patients ≥70 years old	Comorbidities: Caution should be used in patients with compromised bone marrow reserve due to increased risk of hematologic toxicity Caution should be used in patients with a history of pre-existing conditions including peripheral neuropathy, falls due to increased risk for neuropathy Polypharmacy: Minimize exposure to QTc-prolonging agents Nutrition: Electrolyte imbalances (magnesium and potassium) should be corrected prior to initiation and

(*continued on next page*)

Table 5 (*continued*)

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
Ixabepilone [159–160]	No adjustment required for pre-existing mild to severe renal impairment	For monotherapy, no dose adjustment is required for mild hepatic impairment (AST and ALT ≤2.5 times ULN and bilirubin ≤1 times ULN). Reduce dose to 32 mg/m^2 or moderate hepatic impairment (AST and ALT >2.5 to ≤10 times ULN and bilirubin >1 to ≤1.5 times ULN). Reduce dose to 20 mg/m^2, titrate to 30 mg/m^2 if tolerated, for severe hepatic impairment (AST and ALT ≤10 times ULN and bilirubin >1.5 to ≤3 times ULN)·Use is not recommended for AST or ALT >10 times ULN or bilirubin >3 times ULN. For combination therapy with capecitabine, no adjustment is required for mild hepatic impairment (AST and ALT ≤2.5 x ULN and bilirubin ≤1 x ULN). Use is contraindicated with moderate to severe hepatic impairment (AST or ALT >2.5 x ULN or bilirubin >1 x ULN)	Vahdat et al. retrospectively evaluated the safety and efficacy of ixabepilone and capecitabine (n = 116) versus capecitabine alone (n = 135) in 251patients aged ≥65 years compared to younger patients aged <65 years. Efficacy was similar between patients aged ≥65 and young patients aged <65 years. Grade 3/4 hematologic toxicity was similar in both groups yet a higher incidence of leukopenia (18% vs. 8%) and febrile neutropenia (10% vs. 5%) were noted in the elderly. Grade 3/4 non-hematologic toxicities were similar between groups except for a higher incidence of asthenia (14% vs. 6%), stomatitis (5% vs. 1%), and anorexia (5% vs. 1%) in the elderly	during therapy Comorbidities: Caution should be used in patients with compromised bone marrow reserve due to increased risk of hematologic toxicity Caution should be used in patients with a history of pre-existing conditions including peripheral neuropathy, falls due to increased risk for neuropathy Polypharmacy: Avoid concurrent use with strong CYP3A4 inhibitors. It co-administration cannot be avoided, consider a dose reduction of ixabepilone to 20 mg/m^2. When the strong CYP3A4 inhibitor is discontinued, allow 1 week prior to before the dose is adjusted back up to the indicated dose Avoid concurrent use with strong CYP3A4 inducers. If co-administration cannot be avoided, the dose of ixabepilone may need to be gradually titrated up from 40 mg/m^2 to 60 mg/m^2, based on tolerance. When the strong CYP3A4 inducer is discontinued, reduce the dose back to prior to initiation
Nabpaclitaxel [161–162]	No adjustment required for pre-existing mild to severe renal impairment. Has not been studied	No dose adjustment is required for patients with mild hepatic impairment (total bilirubin ≤ 1.5 x ULN and AST ≤ 10 x ULN). Dose adjustments are required for moderate to severe hepatic impairment. Does adjustments are dependent on indication	In a clinical trial of 981 patients who received nab-paclitaxel monotherapy for metastatic breast cancer, 15% of patients were aged ≥65 and 2% were aged ≥75 years old. A higher incidence of epistaxis, diarrhea, dehydration, fatigue, and peripheral edema was found in older patients compared to younger patients In a clinical trial of 514 patients who received nab-paclitaxel combined with carboplatin for NSCLC, 31% of patients were aged ≥65 and 3.5% were aged ≥75 years old. No differences were observed in efficacy between the age groups. A higher incidence of myelosuppression, peripheral neuropathy, and arthralgia were noted in older patients compared to younger patients In a clinical trial of 431 patients who received nab-paclitaxel combined with gemcitabine for pancreatic cancer, 41% of patients were aged ≥65 and 10% were ≥75 years old. No differences were observed in efficacy between the age groups. A higher incidence of diarrhea, decreased appetite, dehydration, and epistaxis were noted in older patients compared to younger patients	Comorbidities: Caution should be used in patients with compromised bone marrow reserve due to increased risk of hematologic toxicity Caution should be used in patients with a history of pre-existing conditions including peripheral neuropathy, falls due to increased risk for neuropathy Polypharmacy: Avoid concurrent use with CYP2C8 or CYP3A4 inhibitors or inducers
Topoisomerase inhibitors				
Bleomycin [163–164]	No adjustment required for pre-existing mild renal impairment (CrCl ≥50 mL/min). Reduce dose to 70% for CrCl 40–50 mL/min. Reduce dose to 60% for CrCl 30–40 mL/min. Reduce dose to 55% for CrCl 20–30	No adjustments were provided (has not been studied)	In clinical trials, pulmonary toxicity was more common in patients older than 70 years than in younger patients Stamatoullas et al. conducted a	Comorbidities: Caution should be used in patients with a history pulmonary disease due to increased risk for pulmonary toxicity Caution should be used in patients

Table 5 (*continued*)

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
	mL/min. Reduce dose to 45% for CrCl 10–20 mL/min. Reduce dose to 40% for CrCl 5–10% mL/min		retrospective review 147 patients aged ≥60 years with Hodgkin lymphoma who received ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) to assess efficacy and toxicity. Treatment modification was applied in 56 patients for toxicity or progression. Bleomycin was removed or reduced in 53 patients, mainly for pulmonary toxicity. One hundred and seventeen patients achieved a complete remission, 6 a partial remission, 16 had refractory disease and 8 were non-evaluable. Five-year overall survival was estimated at 67%. ABVD was demonstrated to be effective in elderly patients with an increased frequency of pulmonary events	with a history of renal impairment due to the increased risk of toxicity
Daunorubicin [165–167]	No adjustment required for pre-existing mild to moderate renal impairment. Administer 50% of the normal dose for severe renal impairment (SrCr >3 mg/dL)	Reduce starting dose by 25% for mild to moderate hepatic impairment (bilirubin 1.2 to 3 mg/dL). Reduce dose by 50% for severe hepatic impairment (bilirubin >3 mg/dL)	Reported clinical experience has not identified differences in effectiveness between elderly and younger patients. Appropriate studies with daunorubicin hydrochloride have not been performed in the geriatric population, cardiotoxicity may be more frequent in the elderly Löwenberg et al. prospectively evaluated newly diagnosed patients with acute myeloid leukemia who were randomized to conventional dose versus escalated dose daunorubicin. The complete remission rates were 64% in the dose-escalated group and 54% in the conventional-dose group ($P = .002$). The rates of remission after the first cycle of induction treatment were 52% and 35%, respectively ($P < .001$). There was no significant difference between the two groups in the incidence of hematologic toxic effects, 30-day mortality (11% and 12% in the two groups, respectively), or the incidence of moderate, severe, or life-threatening adverse events ($P = .08$) Aapro et al. developed a position paper on the use of anthracyclines in elder cancer patients and reported that age itself should not prevent access to potentially curative treatment or treatment that prolongs life or improves its quality. A comprehensive assessment of risk for cardiotoxicity The risk of cardiotoxicity with conventional anthracyclines should be assessed because cumulative and irreversible cardiotoxicity is likely to be greater in older adults than among younger patients. Use of liposomal anthracycline formulations, prolonging the infusion time for conventional anthracyclines and cardio-protective measures should be considered	Comorbidities: Caution should be used in patients with a history of coronary artery disease, hypertension, myocardial infarction, ischemia, and arrhythmias, due to increased risk of cardiotoxicity Caution should be used in patients with a history of renal and/or hepatic impairment due to an increased risk of toxicity
Doxorubicin [168–169]	No adjustment required for pre-existing mild to severe renal impairment	Reduce starting dose by 50% for mild to moderate hepatic impairment (bilirubin 1.2 to 3 mg/dL). Reduce dose by 75% for severe hepatic	An estimated 4600 patients who were 65 and over were included in the reported clinical experience of doxorubicin use for various	Comorbidities: Caution should be used in patients with a history of coronary artery disease, hypertension, myocardial infarction,

(*continued on next page*)

Table 5 (*continued*)

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
		impairment (bilirubin 3.1 to 5 mg/dL). Severe hepatic impairment (Child-Pugh C or bilirubin >5 mg/dL), avoid use	indications. No overall differences in safety and effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out Ibrahim et al. conducted a retrospective study of 1011 patients with metastatic breast cancer to assess tolerance and toxicity of doxorubicin-containing regimens. Seven hundred sixty-seven patients aged between 50 and 64 years were identified. While the response rate was higher in the younger group, the overall survival curves were similar for the two groups ($P = .06$), as well as the time to progression of the disease ($P = .15$). The dose intensity was comparable between the groups ($P = .49$), as was the median platelet and white blood cell nadirs. Neutropenic fever occurred in 16% of each group ($P = 83$), and fever in 12% and 17% of each group, respectively ($P = .05$). Death from infection occurred in 3.1% and 3.2% of patients in the two groups ($P = .82$)	ischemia, and arrhythmias, due to increased risk of cardiotoxicity Caution should be used in patients with a history of hepatic impairment due to an increased risk of toxicity
Irinotecan [134, 170–172]	No adjustments were provided (has not been studied)	Reduce initial dose by one dose level for mild to moderate hepatic impairment (bilirubin > ULN to ≤2 mg/dL). Avoid use with bilirubin >2 mg/dL. Floyd et al. proposed recommendations for patients with pre-existing hepatic impairment – reduce dose by 25% for mild-moderate impairment (bilirubin 1.5 to 3 mg/dL).	A dose reduction is recommended for patients aged ≥70 years of age receiving the every-3-week regimen. The frequency of grade 3/4 late diarrhea by age was significantly greater in patients ≥65 years than in patients <65 years (40% [53/133] versus 23% [40/171]; $p = .002$). In another study of 183 patients treated on the weekly schedule, the frequency of grade 3/4 late diarrhea in patients ≥65 years of age was 28.6% [26/91] and in patients <65 years of age was 23.9% [22/92] Folprecht et al. conducted a combined analysis of phase 3 trials using fluorouracil versus fluorouracil plus irinotecan in the first-line setting for colorectal cancer to evaluate the efficacy and safety in elderly (aged ≥70 years; $n = 599$) compared with younger (age < 70 years; $n = 2092$) patients. Response rates were improved with irinotecan-based combination therapy compared with fluorouracil monotherapy in patients both younger than 70 years and ≥ 70 years (46.6% v 29.0% $P < .0001$; and 50.5% v 30.3%, $P < .0001$, respectively). With irinotecan/FU, progression-free survival was better for both younger (hazard ratio [HR], 0.77; 95% CI, 0.70 to 0.85; $P < .0001$) and elderly patients (HR, 0.75; 95% CI, 0.61 to 0.90; $P = .0026$). A significant interaction between treatment and age (cutoff, 70 years) for vomiting and hepatotoxicity was not confirmed by analysis that used age as a continuous variable Sasaki et al. retrospectively evaluated the effects of concomitant	Comorbidities: Caution should be used in patients with a history of hepatic impairment due to an increased risk of toxicity Polypharmacy: Caution should be used in patients taking multiple concomitant medications due to an increased risk of severe irinotecan-related toxicity Avoid concurrent use with strong CYP3A4 inhibitors and/or inducers (e.g., St. John's Wort is an enzyme inducer that can decrease exposure to irinotecan and SN-38, the active metabolite). Enzyme inhibitors may increase exposure and lead to increased toxicity

Table 5 (*continued*)

Drugs	Renal adjustment	Hepatic adjustment	Toxicity and outcomes data based on chronologic age	Considerations for use based on select geriatric assessment domains
			medications and polypharmacy on adverse reactions related to irinotecan-based therapy. Of the 172 patients, 118 received concomitant medications. Multiple concomitant medications were significantly related to severe irinotecan-related toxicity in patients receiving monotherapy or fluorouracil plus irinotecan combination therapy ($P = .01$). The incidence of severe irinotecan-related toxicities increased in parallel with the number of concomitant medications	
Vinca Alkaloid Vincristine [173–174]	No adjustment required for pre-existing mild to severe renal impairment	Reduce the dose by 50% for pre-existing hepatic impairment (serum bilirubin >3 mg/dL) based on the package insert Floyd et al. proposed dosing recommendations for patients with pre-existing hepatic impairment. Reduce the dose by 50% for hepatic impairment (serum bilirubin 1.5 to 3 mg/dL or transaminases 2 to 3 times ULN or alkaline phosphatase increased)	Tirelli et al. reported results of the European Organization for Research and Treatment of Cancer Lymphoma Groups which compared chemotherapy designed for elderly patients (etoposide, mitoxantrone, prednimustine) versus the standard (cyclophosphamide, doxorubicin, vincristine, and prednisone) in patients aged ≥70 years old with non-Hodgkin lymphoma. CHOP remains the standard of care for patients aged ≥70 years with NHL	Comorbidities: Caution should be used in patients with a history of pre-existing neurologic conditions including confusion, depression peripheral neuropathy, falls due to increased risk for neurotoxicity Polypharmacy: Avoid concurrent use with CYP3A4 inhibitors due to increased risk for toxicity

Author Contributions

Study concepts	Ginah Nightingale
Study design	Ginah Nightingale
Data acquisition	Ginah Nightingale, Rowena Schwartz, Ekaterina Kachur, Brianne N. Dixon, Christine Cote, Ashley Barlow, Brooke Barlow, Patrick Medina
Quality control and algorithms	Ginah Nightingale
Data analysis and interpretation	Ginah Nightingale, Rowena Schwartz, Ekaterina Kachur, Brianne N. Dixon, Christine Cote, Ashley Barlow, Brooke Barlow, Patrick Medina
Statistical analysis	Not applicable
Manuscript preparation	Ginah Nightingale, Rowena Schwartz, Ekaterina Kachur, Brianne N. Dixon, Christine Cote, Ashley Barlow, Brooke Barlow, Patrick Medina
Manuscript editing	Ginah Nightingale
Manuscript review	Ginah Nightingale, Rowena Schwartz, Ekaterina Kachur, Brianne N. Dixon, Christine Cote, Ashley Barlow, Brooke Barlow, Patrick Medina

Disclosures

There was no sponsorship for this study.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66(1):7–30.
[2] Scher KS, Hurria A. Under-representation of older adults in cancer registration trials: known problem, little progress. J Clin Oncol 2012;30(17):2036–8.
[3] Le Saux O, Falandry C, Gan HK, You B, Freyer G, Péron J. Inclusion of elderly patients in oncology clinical trials. Ann Oncol 2016;27(9):1799–804.
[4] Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. J Clin Oncol 2004;22(22):4626–31.
[5] Levit LA, Balogh E, Nass SJ, Ganz P, editors. Delivering high-quality cancer care: Charting a new course for a system in crisis. Washington, DC: National Academies Press; 2013 Dec..
[6] Hurria A, Levit LA, Dale W, Mohile SG, Muss HB, Fehrenbacher L, et al. Improving the evidence base for treating older adults with cancer: American Society of Clinical Oncology statement. J Clin Oncol 2015;33(32):3826–33.
[7] Network National Comprehensive Cancer. NCCN Clinical Practice Guidelines in Oncology: Older Adult Oncology [Accessed September 1, 2017].
[8] Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen ML, Extermann M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol 2014;32(24):2595–603.
[9] Rubenstein LZ, Stuck AE, Siu AL, Wieland D. Impacts of geriatric evaluation and management programs on defined outcomes: overview of the evidence. J Am Geriatr Soc 1991;39(9 Pt 2):8S–16S [discussion 7S-8S].
[10] Hurria A, Lichtman SM. Clinical pharmacology of cancer therapies in older adults. Br J Cancer 2008;98(3):517.
[11] Gonsalves W, Ganti AK. Targeted anti-cancer therapy in the elderly. Crit Rev Oncol Hematol 2011;78(3):227–42.
[12] Shi S, Mörike K, Klotz U. The clinical implications of ageing for rational drug therapy. Eur J Clin Pharmacol 2008;64(2):183–99.
[13] Korc-Grodzicki B, Boparai MK, Lichtman SM. Prescribing for older patients with cancer. Clin Adv Hematol Oncol 2014;12(5):309–18.
[14] Kinirons MT, O'Mahony MS. Drug metabolism and ageing. Br J Clin Pharmacol 2004;57(5):540–4.
[15] Schmucker DL. Liver function and phase I drug metabolism in the elderly: a paradox. Drugs Aging 2001;18(11):837–51.
[16] Venook AP, Enders Klein C, Fleming G, Hollis D, Leichman CG, Hohl R, et al. A phase I and pharmacokinetic study of irinotecan in patients with hepatic or renal dysfunction or with prior pelvic radiation: CALGB 9863. Ann Oncol 2003;14(12):1783–90.
[17] U.S. Department of Health and Human Services Food and Drug Administration. Guidance for industry: Pharmacokinetics in patients with impaired hepatic function: Study design, data analysis, and impact on dosing and labeling. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072123.pdf, Accessed date: 9 April 2018.
[18] Popa MA, Wallace KJ, Brunello A, Extermann M, Balducci L. Potential drug interactions and chemotoxicity in older patients with cancer receiving chemotherapy. J Geriatr Oncol 2014;5:307–14.
[19] Riechelmann RP, Tannock IF, Wang L, et al. Potential drug interactions and duplicate prescriptions among cancer patients. J Natl Cancer Inst 2007;99:592–600.
[20] Nightingale G, Pizzi LT, Barlow A, Barlow B, Jacisin T, McGuire M, et al. The prevalence of major drug-drug interactions in older adults with cancer and the role of clinical decision support software. J Geriatr Oncol 2018 Mar 3. https://doi.org/10.1016/j.jgo.2018.02.001.

[21] Scripture CD, Figg WD. Drug interactions in cancer therapy. Nat Rev Cancer 2006;6(7):546.
[22] Riechelmann RP, Del Giglio A. Drug interactions in oncology: how common are they? Ann Oncol 2009;20(12):1907–12.
[23] Segal EM, Flood MR, Mancini RS, Whiteman RT, Friedt GA, Kramer AR, et al. Oral chemotherapy food and drug interactions: a comprehensive review of the literature. J Oncol Pract 2014;10(4):e255–68.
[24] Jamani R, Lee EK, Berry SR, et al. High prevalence of potential drug-drug interactions in patients with castration-resistant prostate cancer treated with abiraterone acetate. Eur J Clin Pharmacol 2016;72(11):1391–9.
[25] Lichtman SM, Wildiers H, Launay-Vacher V, Steer C, Chatelut E, Aapro M. International Society of Geriatric Oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency. Eur J Cancer 2007;43(1):1.
[26] Muss HB, Berry DA, Cirrincione C, Budman DR, Henderson IC, Citron ML, et al. Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: the Cancer and Leukemia Group B Experience. J Clin Oncol 2007;25(24):3699–704.
[27] Owyong M, Efe G, Owyong M, Abbasi AJ, Sitarama V, Plaks V. Overcoming barriers of age to enhance efficacy of cancer immunotherapy: the clout of the extracellular matrix. Front Cell Dev Biol 2018;6:19.
[28] Alecensa (alectinib) [prescribing information]. South San Francisco, CA: Genentech USA, Inc.; November 2016.
[29] Hida T, Nokihara H, Kondo M, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet 2017;390(10089):29–39.
[30] Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus crizotinib in untreated ALK-positive non–small-cell lung cancer. N Engl J Med 2017;377(9):829–38.
[31] Alunbrig (brigatinib) [prescribing information]. Cambridge, MA: Ariad Pharmaceuticals Inc; April 2017.
[32] Kim DW, Tiseo M, Ahn MJ, Reckamp KL, Hansen KH, Kim SW, Huber RM, West HL, Groen HJ, Hochmair MJ, Leighl NB. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. J Clin Oncol 2017;35(22):2490–8.
[33] Zykadia (ceritinib) [prescribing information]. East Hanover, NJ: Novartis; July 2017.
[34] Xalkori (crizotinib) [prescribing information]. New York, NY: Pfizer Labs; July 2017.
[35] Blackhall F, Shaw A, Janne PA, et al. Crizotinib safety profile in elderly and non-elderly patients with advanced ALK+ non-small cell lung cancer. Proc IASCL: abstr P1; 2013. p. 11–017.
[36] Bosulif (bosutinib) [prescribing information]. New York, NY: Pfizer Labs; April 2017.
[37] Cortes JE, Kim DW, Kantarjian HM, et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: results from the BELA trial. J Clin Oncol 2012;30:3486–92.
[38] Sprycel (dasatinib) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; August 2017.
[39] Latagliata R, Breccia M, Castagnetti F, et al. Dasatinib is safe and effective in unselected chronic myeloid leukaemia elderly patients resistant/intolerant to imatinib. Leuk Res 2011 Sep;35(9):1164–9.
[40] Gleevec (imatinib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals; received; April 2017.
[41] Latagliata R, Ferrero D, Iurlo A, et al. Imatinib in very elderly patients with chronic myeloid leukemia in chronic phase: a retrospective study. Drugs Aging 2013 Aug;30(8):629–37.
[42] Iurlo A, Nobili A, Latagliata R, et al. Imatinib and polypharmacy in very old patients with chronic myeloid leukemia: effects on response rate, toxicity and outcome. Oncotarget 2016;7(48):80083–90.
[43] Tasigna (nilotinib) [prescribing information]. East Hanover, NJ: Novartis; February 2017.
[44] Lipton JH, le Coutre PD, Wang J, et al. Nilotinib in elderly chronic myeloid leukemia patients in chronic phase (CML-CP) with imatinib resistance or intolerance: efficacy and safety analysis. Blood 2008;112:3233.
[45] Giles FJ, Rea D, Rosti G, et al. Impact of age on efficacy and toxicity of nilotinib in patients with chronic myeloid leukemia in chronic phase: ENEST1st subanalysis. J Cancer Res Clin Oncol 2017 Mar 31. https://doi.org/10.1007/s00432-017-2402-x [Epub ahead of print].
[46] Iclusig (ponatinib hydrochloride) [prescribing information]. Cambridge, MA: ARIAD Pharmaceuticals Inc; November 2016.
[47] Cortes JE, Kim DW, Pinilla-Ibarz J, et al. PACE, a phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med 2013;369:1783–96.
[48] Tafinlar (dabrafenib) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; June 2017.
[49] Ouellet D, Gibiansky E, Leonowens C, et al. Population pharmacokinetics of dabrafenib, a BRAF inhibitor: effect of dose, time, covariates, and relationship with its metabolites. J Clin Pharmacol 2014;54:696–706.
[50] Zelboraf (vemurafenib) [prescribing information]. South San Francisco, CA: Genentech USA Inc; April 2017.
[51] Zhang W, Heinzmann D, Grippo JF. Clin pharmaco kinet. Clin Pharmacokinet Vemurafenib 2017:1–17.
[52] Larkin J, Del Vecchio M, Ascierto PA, Krajsova I, Schachter J, Neyns B, et al. Vemurafenib in patients with BRAF(V600) mutated metastatic melanoma: an open-label, multicentre, safety study. Lancet Oncol 2014;15 [436e44].
[53] Gilotrif (afatinib) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; October 2016.
[54] Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31(27):3327–34.
[55] Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol 2014;15:213–22.
[56] Tarceva (erlotinib) [prescribing information]. South San Francisco, CA: Genetech USA Inc; October 2016.
[57] Wheatley-Price P, Ding K, Seymour L, et al. Erlotinib for advanced non-small-cell lung cancer in the elderly: an analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol 2008 May 10;26(14):2350–7.
[58] Yamada K, Azuma K, Takeshita M, et al. Phase II trial of Erlotinib in elderly patients with previously treated non-small cell lung Cancer: results of the lung oncology Group in Kyushu (LOGiK-0802). Anticancer Res 2016;36(6):2881–7.
[59] Tykerb (lapatinib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2017.
[60] Crown JP, Burris 3rd HA, Boyle F, et al. Pooled analysis of diarrhea events in patients with cancer treated with lapatinib. Breast Cancer Res Treat 2008;112:317–25.
[61] Perez EA, Koehler M, Byrne J, et al. Cardiac safety of lapatinib: pooled analysis of 3689 patients enrolled in clinical trials. Mayo Clin Proc 2008;83:679–86.
[62] Caprelsa (vandetanib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals; December 2016.
[63] Gridelli C, Novello S, Zilembo N, et al. Phase II randomized study of vandetanib plus gemcitabine or gemcitabine plus placebo as first-line treatment of advanced non-small-cell lung cancer in elderly patients. J Thorac Oncol 2014;9(5):733–7.
[64] Cotellic (cobimetinib) [prescribing information]. South San Francisco, CA: Genentech USA, Inc; May 2016.
[65] Mekinist (trametinib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals; June 2017.
[66] Inlyta (axitinib) [prescribing information]. New York, NY: Pfizer Inc; August 2014.
[67] Miyake H, Harada KI, Ozono S, Fujisawa M. Efficacy and safety of axitinib in elderly patients with metastatic renal cell carcinoma. Med Oncol 2016;33(8):95.
[68] Cabometyx (cabozantinib) [prescribing information]. South San Francisco, CA: Exelixis, Inc; April 2016.
[69] Votrient (pazopanib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; May 2017.
[70] Stivarga (regorafenib) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; April 2017.
[71] Nexavar (sorafenib) [prescribing information]. Wayne, NJ: Bayer HealthCare Pharmaceuticals; November 2013.
[72] Eisen T, Oudard S, Szczylik C, et al. Sorafenib for older patients with renal cell carcinoma: a subset analysis from a randomized trial. J Natl Cancer Inst 2008;100:1454–63.
[73] Sutent (sunitinib) [prescribing information]. New York, NY: Pfizer Labs; April 2015.
[74] Hutson TE, Bukowski RM, Rini BI, Gore ME, Larkin JM, Figlin RA, et al. Efficacy and safety of sunitinib in elderly patients with metastatic renal cell carcinoma. Br J Cancer 2014;110:1125–32.
[75] Kadcyla (ado-trastuzumab) [prescribing information]. South San Francisco, CA: Genentech Inc; July 2016.
[76] Avastin (bevacizumab) [prescribing information]. South San Francisco, CA: Genentech Inc; December 2016.
[77] Blincyto (blinatumomab) [prescribing information]. Thousand Oaks, CA: Amgen Inc; July 2017.
[78] Adcetris (brentuximab vedotin) [prescribing information]. Bothell, WA: Seattle Genetics; September 2016.
[79] Erbitux (cetuximab) [prescribing information]. Indianapolis, IN: Eli Lilly and Company; October 2016.
[80] Darzalex (daratumumab) [prescribing information]. Horsham, PA: Janssen Biotech, Inc; June 2017.
[81] Portrazza (necitumumab) [prescribing information]. Indianapolis, IN: Eli Lilly and Company; November 2015.
[82] Vectibix (panitumumab) [prescribing information]. Thousand Oaks, CA: Amgen; June 2017.
[83] Perjeta (pertuzumab) [prescribing information]. South San Francisco, CA: Genentech Inc; May 2017.
[84] Arzerra (ofatumumab) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals; August 2016.
[85] Cyramza (ramucirumab) [prescribing information]. Indianapolis, IN: Eli Lilly and Company; February 2017.
[86] Rituxan (rituximab) [prescribing information]. South San Francisco, CA: Genentech Inc; March 2016.
[87] Fischer K, Bahlo J, Fink AMM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: Updated results of the CLL8 trial. Blood 2016;127:208–15.
[88] Herceptin (trastuzumab) [prescribing information]. San Francisco, CA: Genetech Inc; April 2017.
[89] Singh JC, Lichtman SM. Targeted agents for HER2-positive breast cancer: optimal use in older adults. Drugs Aging 2015;12:975–82.
[90] Andrews A. Treating with checkpoint inhibitors—figure $1 million per patient. Am Health Drug Benefits 2015 Aug;8(Spec Issue):9.
[91] Tecentriq (atezolizumab) [prescribing information]. South San Francisco, CA: Genentech Inc; April 2017.
[92] Bavencio (avelumab) [prescribing information]. Rockland, MA: EMD Serono Inc; May 2017.
[93] Imfinzi (durvalumab) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; April 2017.
[94] Yervoy (ipilimumab) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; July 2017.

[95] Opdivo (nivolumab) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; September 2017.
[96] Keytruda (pembrolizumab) [prescribing information]. Whitehouse Station, NJ: Merck; July 2017.
[97] Arimidex (anastrozole) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; May 2014.
[98] Abdel-Qadir H, Amir E, Fischer HD, et al. The risk of myocardial infarction with aromatase inhibitors relative to tamoxifen in post-menopausal women with early stage breast cancer. Eur J Cancer 2016;68:11–21.
[99] Tamoxifen citrate [prescribing information]. Corona, CA: Watson Laboratories; July 2011.
[100] Zytiga (abiraterone) [prescribing information]. Horsham, PA: Janssen Biotech Inc; April 2017.
[101] Smith MR, Rathkopf DE, Mulders PF, et al. Efficacy and safety of abiraterone acetate in elderly (75 years or older) chemotherapy naïve patients with metastatic castration resistant prostate cancer. J Urol 2015;194(5):1277–84.
[102] Casodex (bicalutamide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; March 2017.
[103] D'Amico AV, Denham JW, Crook J, et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. J Clin Oncol 2007;25(17):2420–5.
[104] Xtandi (enzalutamide) [prescribing information]. Northbrook, IL: Astellas Pharma US; July 2017.
[105] Firmagon (degarelix) [prescribing information]. Parsippany, NJ: Ferring Pharmaceuticals Inc; July 2016.
[106] Trisenox (arsenic trioxide) [prescribing information]. Frazer, PA: Cephalon, Inc; February 2015.
[107] Zhang Y, Zhang Z, Li J, et al. Long-term efficacy and safety of arsenic trioxide for first-line treatment of elderly patients with newly diagnosed acute promyelocytic leukemia. Cancer 2013;119(1):115–25.
[108] Velcade (bortezomib) [prescribing information]. Cambridge, MA: Millennium Pharmaceuticals Inc; June 2017.
[109] Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Safety and efficacy of bortezomib in high-risk and elderly patients with relapsed multiple myeloma. Br J Hae Matol 2007;137:429–35.
[110] Kyprolis (carfilzomib) [prescribing information]. Thousand Oaks, CA: Onyx Pharmaceuticals Inc; May 2017.
[111] Zortress (everolimus) [prescribing information]. East Hanover, NJ: Novartis Pharmaceutical Co; October 2016.
[112] Pritchard KI, Burris HA, Ito Y, et al. Safety and efficacy of everolimus with exemestane vs. exemestane alone in elderly patients with HER2-negative, hormone receptor-positive breast cancer in BOLERO-2. Clin Breast Cancer 2013;13(6):421–32.
[113] Ninlaro (ixazomib) [prescribing information]. Cambridge, MA: Takeda Pharmaceutical Company Limited; November 2016.
[114] Revlimid (lenalidomide) [prescribing information]. Summit, NJ: Celgene Corporation; February 2017.
[115] Lynparza (olaparib tablets) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals; August 2017.
[116] Ibrance (palbociclib) [prescribing information]. New York, NY: Pfizer Labs; March 2017.
[117] Pomalyst (pomalidomide) [prescribing information]. Summit, NJ: Celgene Corporation; June 2016.
[118] Rubraca (rucaparib) [prescribing information]. Boulder, CO: Clovis Oncology; February 2017.
[119] Torisel (temsirolimus) [prescribing information]. Philadelphia, PA: Pfizer Inc; July 2017.
[120] Levakov I, Vojinov S, Marusic G, et al. Safety profile of temsirolimus in patients with metastatic renal cell carcinoma. J BUON 2016;21(6):1442–8.
[121] Erivedge (vismodegib) [prescribing information]. South San Francisco, CA: Genentech USA; August 2017.
[122] Chang AL, Lewis KD, Arron ST, et al. Safety and efficacy of vismodegib in patients aged ≥ 65 years with advanced basal cell carcinoma. Oncotarget 2016;7(46):76118–24.
[123] Treanda (bendamustine) [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA Inc; October 2016.
[124] Laurenti L, Innocenti I, Autore F, et al. Bendamustine in combination with rituximab for elderly patients with previously untreated B-cell chronic lymphocytic leukemia: a retrospective analysis of real-life practice in Italian hematology departments. Leuk Res 2015;39:1068–70.
[125] Busulfex (busulfan) [prescribing information]. Greenville, NC: DSM Pharmaceuticals; January 2015.
[126] Paraplatin (carboplatin) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Co; July 2010.
[127] Ramalingman S, Perry MC, La Rocca RV, et al. Comparison of outcomes for elderly patients treated with weekly paclitaxel in combination with carboplatin versus the standard 3- weekly paclitaxel and carboplatin for advanced non-small cell lung cancer. Cancer 2008;113(3):542–6.
[128] Cisplatin [prescribing information]. Durham, NC: Accord; October 2015.
[129] Lichtman SM, Buchholtz M, Marino J, et al. Use of cisplatin for elderly patients. Age Aging 1992;21(3):202–4.
[130] Hrushesky WJ, Shimp W, Kennedy BJ. Lack of age-dependent cisplatin nephrotoxicity. Am J Med 1984;76(4):579–84.
[131] Cubillo A, Cornide M, Lopez JL, et al. Renal tolerance to cisplatin in patients 70 years and older. Am J Clin Oncol 2001;24(2):192–7.
[132] Aronoff GR, Bennett WM, Berns JS, et al. Drug prescribing in renal failure: Dosing guidelines for adults and children. 5th ed., vol. 100, Philadelphia, PA: American College of Physicians; 2007; 172.
[133] Cyclophosphamide Injection [prescribing information]. Deerfield, IL: Baxter; June 2015.
[134] Floyd J, Mirza I, Sachs B, et al. Hepatotoxicity of chemotherapy. Semin Oncol 2006; 33(1):50–67.
[135] Wildiers H, Highley MS, de Bruijin EA, van Oosterom AT. Pharmacology of anticancer drugs in the elderly population. Clin Pharmacokinet 2003;42:1213–42.
[136] Ifex (ifosfamide) [prescribing information]. Deerfield, IL: Baxter Healthcare Corporation; August 2014.
[137] De Pas T, Curigliano G, Catania C, et al. Ifosfamide in the elderly: clinical considerations for a better drug management. Crit Rev Oncol Hematol 2000;33:129–35.
[138] Eloxatin (oxaliplatin) [prescribing information]. Bridgewater, NJ: Sanofi-Aventis; October 2015.
[139] Baek KK, Lee J, Park, et al. Oxaliplatin-induced chronic peripheral neurotoxicity: a prospective analysis in patients with colorectal cancer. Cancer Res Treat 2010;42: 185–90.
[140] Goldberg RM, Tabah-Fisch I, Bleiberg H, de Gramont A, Tournigand C, Andre T, et al. Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer. J Clin Oncol 2006; 24:4085–91.
[141] Xeloda (capecitabine) [prescribing information]. South San Francisco, CA: Genentech USA, Inc; December 2016.
[142] Ershler WB. Capecitabine use in geriatric oncology: an analysis of current safety, efficacy, and quality of life data. Crit Rev Oncol Hematol 2006;58(1):68–78.
[143] Feliu J, Escudero P, Llosa F, Bolaños M, Vicent JM, Yubero A, et al. Capecitabine as first-line treatment for patients older than 70 years with metastatic colorectal cancer: an oncopaz cooperative group study. J Clin Oncol 2005;23(13):3104–11.
[144] Bajetta E, Procopio G, Celio L, Gattinoni L, Della Torre S, Mariani L, et al. Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. J Clin Oncol 2005;23(10):2155–61.
[145] Cytarabine (prescribing information). Rockford, IL: Mylan Institutional; December 2013.
[146] Lindner LH, Ostermann H, Hiddemann W, Kiani A, Würfel M, Illmer T, et al. AraU accumulation in patients with renal insufficiency as a potential mechanism for cytarabine neurotoxicity. Int J Hematol 2008;88(4):381–6.
[147] Adrucil (fluorouracil injection) [prescribing information]. North Wales, PA: Teva Pharmaceuticals Inc; November 2016.
[148] Lim KH, Lee HY, Park SB, Song SY. Feasibility of Modified FOLFOX in Elderly Patients Aged ≥ 80 Years with Metastatic Gastric Cancer or Colorectal Cancer. Oncology 2017;93(2):115–21.
[149] Folprecht G, Cunningham D, Ross P, Glimelius B, Di Costanzo F, Wils J, et al. Efficacy of 5-fluorouracil-based chemotherapy in elderly patients with metastatic colorectal cancer: a pooled analysis of clinical trials. Ann Oncol 2004 Sep 1;15(9):1330–8.
[150] Methotrexate injection (prescribing information). Lake Forest, IL: Hospira Inc; November 2014.
[151] Zhu JJ, Gerstner ER, Engler DA, Mrugala MM, Nugent W, Nierenberg K, et al. High-dose methotrexate for elderly patients with primary CNS lymphoma. Neuro Oncol 2009;11(2):211–5.
[152] Alimta (pemetrexed) [prescribing information]. Indianapolis, IN: Eli Lilly and Company; February 2015.
[153] Paz-Ares LG, Zimmermann A, Ciuleanu T, Bunn PA, San Antonio B, Denne J, et al. Meta-analysis examining impact of age on overall survival with pemetrexed for the treatment of advanced non-squamous non-small cell lung cancer. Lung Cancer 2017;104:45–51.
[154] Hata A, Katakami N, Hattori Y, Tanaka K, Fujita S, Kotani Y, et al. Pemetrexed monotherapy for chemo-naïve elderly (aged≥ 80) patients with non-squamous non-small cell lung cancer: results from combined analysis of two single arm phase II studies (HANSHIN002 and 003). Cancer Chemother Pharmacol 2017;79(4): 689–95.
[155] Folotyn (pralatrexate) [prescribing information]. Westminster, CO: Allos Therapeutics Inc; November 2016.
[156] Jevtana (cabazitaxel) [prescribing information]. Bridgewater, NJ: sanofi-aventis U.S. LLC; September 2017.
[157] Halaven (eribulin) [prescribing information]. Woodcliff Lake, NJ: Eisai; January 2016.
[158] Muss H, Cortes J, Vahdat LT, et al. Eribulin monotherapy in patients aged 70 years and older with metastatic breast Cancer. Oncologist 2014;19:318–27.
[159] Ixempra (ixabepilone) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; October 2011.
[160] Vahdat LT, Vrdoljak E, Gomez H, et al. Efficay and safety of ixabepilone plus capecitabine in eldery patients with anthracycline and taxane pretreated metastatic breast cancer. J Geriatric Oncol 2013;4(4):352–436.
[161] Abraxane (paclitaxel protein bound) [prescribing information]. Summit, NJ: Celgene Corporation; July 2015.
[162] Jin F, Ahu H, Shi F, Kong L, Yu J. A retrospective analysis of safety and efficacy of weekly nab-paclitaxel as second-line chemotherapy in elderly patients with advanced squamous non-small cell lung carcinoma. Clin Interv Aging 2016;11: 167–73.
[163] Bleomycin [prescribing information]. North Wales, PA: Teva Pharmaceuticals; February 2016.
[164] Stamatoullas A, Brice P, Bouabdallah R, Mareschal S, Camus V, Rahal I, et al. Outcome of patients older than 60 years with classical Hodgkin lymphoma treated with front line ABVD chemotherapy: frequent pulmonary events suggest limiting the use of bleomycin in the elderly. Br J Haematol 2015 Jul 1;170 (2):179–84.
[165] Daunorubicin (prescribing information). Bedford, OH: Bedford Laboratories; June 2013.

[166] Löwenberg B, Ossenkoppele GJ, van Putten W, Schouten HC, Graux C, Ferrant A, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. N Engl J Med 2009 Sep 24;361(13):1235–48.
[167] Aapro M, Bernard-Marty C, Brain EG, Batist G, Erdkamp F, Krzemieniecki K, et al. Anthracycline cardiotoxicity in the elderly cancer patient: a SIOG expert position paper. Ann Oncol 2010;22(2):257–67.
[168] Adriamycin (doxorubicin) [prescribing information]. Bedford, OH: Bedford Laboratories; April 2012.
[169] Ibrahim NK, Frye DK, Buzdar AU, Walters RS, Hortobagyi GN. Doxorubicin-based chemotherapy in elderly patients with metastatic breast cancer: tolerance and outcome. Arch Intern Med 1996 Apr 22;156(8):882–8.
[170] Camptosar (irinotecan) [prescribing information]. New York, NY: Pharmacia & Upjohn; April 2016.
[171] Folprecht G, Seymour MT, Saltz L, Douillard JY, Hecker H, Stephens RJ, et al. Irinotecan/fluorouracil combination in first-line therapy of older and younger patients with metastatic colorectal cancer: combined analysis of 2,691 patients in randomized controlled trials. J Clin Oncol 2008;26(9):1443–51.
[172] Sasaki T, Fujita KI, Sunakawa Y, Ishida H, Yamashita K, Miwa K, et al. Concomitant polypharmacy is associated with irinotecan-related adverse drug reactions in patients with cancer. Int J Clin Oncol 2013;18(4):735–42.
[173] Vincristine sulfate [prescribing information]. Lake Forest, IL: Hospira Inc; March 2013.
[174] Tirelli U, Van Glabbeki EM, Teodorovic I, et al. CHOP is the standard regimen in patients ≥ 70 years of age with intermediate-grade and high-grade non-Hodgkin's lymphoma: results of a randomized study of the European Organization for Research and Treatment of Cancer lymphoma cooperative study group. J Clin Oncol 1998;16:27–34.
[175] Sargent DJ, Goldberg RM, Jacobson SD, Macdonald JS, Labianca R, Haller DG, et al. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. N Engl J Med 2001;345(15):1091–7.
[176] Jorgensen ML, Young JM, Solomon MJ. Adjuvant chemotherapy for colorectal cancer: age differences in factors influencing patients' treatment decisions. Pat Prefer Adher 2013;7:827–34.
[177] Ananda S, Field KM, Kosmider S, Compston D, Desai J, Lim LC, et al. Patient age and comorbidity are major determinants of adjuvant chemotherapy use for stage III colon cancer in routine clinical practice. J Clin Oncol 2008;26(27):4516–7.
[178] Wedding U, Ködding D, Pientka L, Steinmetz HT, Schmitz S. Physicians' judgement and comprehensive geriatric assessment (CGA) select different patients as fit for chemotherapy. Crit Rev Oncol Hematol 2007;64(1):1–9.
[179] Linn BS, Linn MW, Gurel LE. Cumulative illness rating scale. J Am Geriatr Soc 1968; 16(5):622–6.
[180] Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol 2011;29(25):3457–65.
[181] American Geriatrics Society. Updated beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2015;63(11):2227–46.
[182] O'Mahony D, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing 2015;44(2):213–8.
[183] Nightingale G, Hajjar E, Swartz K, Andrel-Sendecki J, Chapman A. Evaluation of a pharmacist-led medication assessment used to identify prevalence of and associations with polypharmacy and potentially inappropriate medication use among ambulatory senior adults with cancer. J Clin Oncol 2015;33(13):1453–9.
[184] Prithviraj GK, Koroukian S, Margevicius S, et al. Patient characteristics associated with polypharmacy and inappropriate prescribing of medications among older adults with cancer. J Geriatr Oncol 2012;3:228–2373.
[185] Turner JP, Jamsen KM, Shakib S, Singhal N, Prowse R, Bell JS. Polypharmacy cut-points in older people with cancer: how many medications are too many? Support Care Cancer 2016;24(4):1831–40.
[186] Maggiore RJ, Dale W, Gross CP, et al. Polypharmacy and potentially inappropriate medication use in older adults with cancer undergoing chemotherapy: effect on chemotherapy-related toxicity and hospitalization during treatment. J Am Geriatr Soc 2014;62(8):1505–12.
[187] Bushardt RL, Massey EB, Simpson TW, Ariail JC, Simpson KN. Polypharmacy: misleading, but manageable. Clin Interv Aging 2008;3(2):383–9.
[188] Dimitrow MS, Airaksinen MS, Kivelä SL, et al. Comparison of prescribing criteria to evaluate the appropriateness of drug treatment in individuals aged 65 and older: a systematic review. J Am Geriatr Soc 2011;59(8):1521–30.
[189] Maggiore RJ, Gross CP, Togawa K, Tew WP, Mohile SG, Owusu C, et al. Use of complementary medications among older adults with cancer. Cancer 2012;118: 4815–23.
[190] Wyatt GK, Friedman LL, Given CW, Given BA, Beckrow KC. Complementary therapy use among older cancer patients. Cancer Pract 1999;7:136–44.
[191] Nightingale G, Hajjar E, Guo K, Komura S, Urnoski E, Sendecki J, et al. A pharmacist-led medication assessment used to determine a more precise estimation of the prevalence of complementary and alternative medication (CAM) use among ambulatory senior adults with cancer. J Geriatric Oncol 2015;6(5):411–7.
[192] Nightingale G, Skonecki E, Boparai MK. The impact of polypharmacy on patient outcomes in older adults with cancer. Cancer J 2017;23(4):211–8.
[193] Girre V, Arkoub H, Puts MT, et al. Potential drug interactions in elderly cancer patients. Crit Rev Oncol Hematol 2011;78(3):220–6.
[194] Verbrugghe M, Verhaeghe S, Lauwaert K, et al. Determinants and associated factors influencing medication adherence and persistence to oral anticancer drugs: a systematic review. Cancer Treat Rev 2013;39(6):610–21.
[195] Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care 1986;24:67–74.
[196] MacLaughlin EJ, Raehl CL, Treadway AK, Sterling TL, Zoller DP, Bond CA. Assessing medication adherence in the elderly. Drugs Aging 2005;22(3):231–55.
[197] Hurria A, Mohile S, Gajra A, Klepin H, Muss H, Chapman A, et al. Validation of a prediction tool for chemotherapy toxicity in older adults with cancer. J Clin Oncol 2016;34(20):2366–71.
[198] Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, Defelice J, et al. Predicting the risk of chemotherapy toxicity in older patients: the chemotherapy risk assessment scale for high-age patients (CRASH) score. Cancer 2012;118(13):3377–86.