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Effect of age on drug metabolism in women with breast cancer

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Abstract

Introduction—The aging of the population will increase the number of breast cancer patients requiring treatment in both the adjuvant and metastatic setting. Hormones, chemotherapy and targeted drugs all have a role in treatment. Older patients have been underrepresented in clinical trials making evidence-based decisions difficult. The increase in comorbidity and aging, polypharmacy and changes in function make pharmacotherapy decisions more complicated. Knowledge of the issues is critical in the prescribing of effective and safe therapy. There are factors associated with advancing age that can result in pharmacokinetic and pharmacodynamic variations in processing of hormonal agents, chemotherapy and targeted drugs.

Areas covered—A review of the literature pertaining to pharmacokinetic changes in aging in breast cancer was untaken. Studies are reviewed involving single agents and some combinations.

Expert opinion—Older patients should be considered for standard therapies. Their specific problems need to be evaluated by geriatric-specific assessment including functional status, end organ dysfunction and polypharmacy. There are few instances for age-related changes in pharmacokinetics and when present are usually not clinically significant. When changes are present, they are often the result of comorbidity, drug interactions and drug scheduling issues. The older patients may be more sensitive to certain toxicities such as cardiac toxicity, neuropathy and myelosuppression.

Keywords

CYP450; elderly; geriatrics; pharmacodynamics; pharmacokinetics; polypharmacy; renal insufficiency

1. Introduction

With rapidly expanding aging population in the US as well as the rest of the world, breast cancer is increasingly becoming a disease of the elderly. Most of the clinical trials involving chemotherapeutics, however, focus on younger populations. Although 49% of the breast cancer occurs over the age of 65, only 9% of this population is represented in the clinical trials [1,2]. This is also true of studies of newly approved anticancer therapies [3]. This has

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created a deficiency in the data guiding appropriate selection and management of older breast cancer patients.

National Comprehensive Cancer Network (NCCN) has defined the elderly population as patients aged > 65 years [4]. However, it is usually the patients who are aged > 70 years who are at higher risk of complications from chemotherapy due to comorbidities related to age [5]. There are tools available which can provide some guidance. They include ADJUVANT online. This should be used with caution in women aged > 70 years, as they are based on physician's assessment without taking geriatric parameters such as comorbidity and physical functioning into account. They are likely to overestimate the benefit of chemotherapy in this population leading to overtreatment and increased incidence of chemo-related toxicities and drug interruptions [6].

The cancer and aging research group developed a predictive model for grade 3 – 5 toxicity in geriatric patients using geriatric assessment variables, laboratory test values and patient tumor and treatment characteristics [7]. This model was a better predictive factor for the development of chemotherapy toxicity, when compared to Karnofsky performance status assessment tool or physician judgment. Some salient observations from this study were that greater cumulative toxicity in geriatric population was associated with administering chemotherapy in the seventh decade of life, in gastrointestinal or genitourinary cancers, with the use of polychemotherapy and in patients with preexisting anemia or poor renal function. Functional parameters reflecting poor outcomes with chemotherapy included inability to walk one block, decreased social activity secondary to physical or emotional reasons, history of falls over preceding 6 months and needing assistance with taking medications [5]. NCCN recommends assessment of activities of daily living (ADL) and instrumental ADL in addition to oncology performance status scores while making treatment decisions on elderly cancer patients [4,8].

There a general reluctance in treating elderly breast cancer patients with aggressive multi-agent chemotherapy. This has often resulted in undertreatment [9]. The assumption is that older patients typically present with less aggressive disease (human epidermal growth factor receptor-2 [HER2] negative, hormone positive and lymph node [LN] negative) [10]; however, 21% of triple negative breasts cancer are seen in patients aged >70 years [11]. There is an assumption of poor tolerance to chemotherapy and the desire to avoid drug interactions since these patients are on multiple medications which is common in older patients [12]. The adjuvant chemotherapy in older women (ACTION) trial, which was designed to look at chemotherapy versus observation in elderly patients with hormone receptor negative/weakly positive breast cancer, failed to meet its accrual goals [13]. The ACTION trial was a Phase III trial that planned to randomize 1000 women aged ≥ 70 years with estrogen receptor (ER)-negative or weakly ER-positive breast cancer to receive four cycles of anthracycline chemotherapy or observation. The primary end point was relapse-free interval. The trial failed to recruit because a large number of screened patients were found to be ineligible. Moreover, the small number of eligible patients declined randomization as many older patients refused to accept chemotherapy. These vulnerable, high-risk individuals need chemotherapy and the recognition of pharmacokinetic and pharmacodynamic changes are important to provide safe and effective treatment.

There are increasing data suggesting that older adults with node-positive breast cancer derive similar benefits from standard chemotherapies as the younger patients and such therapies should be offered to them if they are in good health with life expectancies exceeding 5 years [14]. In fact, the very elderly breast cancer populations who are aged > 80 years have worse outcomes if undertreated [15]. The early breast cancer trialists' collaborative group found that breast cancer-related mortality is reduced by one-third with intense adjuvant chemotherapy regimens such as adriamycin/cyclophosphamide/taxol and by 15 – 20% with standard regimens such as adriamycin/cyclophosphamide (AC) or cyclophosphamide/methotrexate/5-fluorouracil (CMF). Patients > 70 years constituted a small group in this meta-analysis, but they appeared to derive the same benefit from chemotherapy as the younger subgroups, although with greater immediate hazards [16]. In a prospective study of women aged > 65 years, standard multi-agent intravenous chemotherapy was found to be superior to a single-agent oral regimen with capecitabine [17].

However, there are some studies which show that the elderly population may derive little benefit from chemotherapy. In an observational study looking at 41,390 women with stage I – III breast cancer who were ≥ 65 years of age, it was found that chemotherapy did not benefit LN-negative or LN-positive ER-positive disease (hazard ratio [HR]: 1.05, 95% confidence interval [CI]: 0.85 – 1.35). However, in elderly patients with LN-positive ER-negative disease, chemotherapy was significantly associated with decreased mortality (HR: 0.72, 95% CI: 0.54 – 0.96). The benefit from chemotherapy also extended to the group aged > 70 years who were LN-positive, ER-negative (HR: 0.74, 95% CI: 0.56 – 0.97). Majority of these patients (> 90%) received either CMF or anthracycline-based combinations [18].

There are also the effects of pharmacokinetic and pharmacodynamic changes that occur with aging particularly over 70 years of age. A significant problem is that the pharmacokinetic studies have primarily involved the younger, healthy patients without significant comorbidity and good performance and functional status. The pharmacokinetic differences based on aging alone have not been great; however, the additive effect of comorbidities can make these differences significant [19]. End organ dysfunction studies have been performed in patients with renal and hepatic dysfunction [20-22]. Studies have also rarely looked at changes over multiple cycles of therapy. Some differences in clinical toxicity have also been the result of drug scheduling and not age [23]. Aging is heterogeneous, creating an even wider variation in pharmacokinetics.

There are some data about age-related changes in absorption. There are changes in splanchnic blood flow, motility and mucosal atrophy [24-26]. The greatest impediment to absorption is compliance. Particularly with the increase in oral therapies, this is an important issue. The problem of polypharmacy in older patients can compound this problem [27-34]. Polypharmacy and inappropriate medication use is an important evaluation in the care of older cancer patients. Polypharmacy can be considered as the current use of many medications or the concurrent use of an excessive number of drugs including non-prescription therapies, often inappropriate for the situation associated with increased risk of adverse drug effects. Its importance lies in its association with problems of compliance due to increased number of pills, regimen complexity and cost issues, increased risk of adverse drug events, increased risk of falls and fractures, cognitive impairment and delirium and

complicates symptom management. The updated Beers criteria divide medication into three clinically relevant categories: drug classes to avoid, drug classes to avoid with certain diseases and syndromes that the drugs can exacerbate and medications to be used with caution [35]. There is a well-documented decline in renal function with age. This is often exacerbated by comorbidity. There are a number of formulae which can aid in the calculation of renal function and can help guide dose modification with renally excreted drugs [36]. These calculations do have their limitations and should be used with care. Guidelines have been published regarding these issues. Of note is that serum creatinine alone is not an adequate guide of renal function [37-39]. In the renal insufficiency and anticancer medications study in 1898 patients with breast cancer, the prevalence of renal insufficiency was 51.8% (creatinine clearance of < 90 ml/min). Renal insufficiency was seen in 87.8% of patients in whose serum creatinine was normal [39]. There are no significantly documented age-related changes in CYP450 activity [40]. The presence of polypharmacy and drug interactions is the more significant factor. Hepatic mass and blood flow decrease with age. The impact of the decline in hepatic mass and blood flow on hepatic enzyme function is uncertain [41,42].

What are often more clinically relevant are the pharmacodynamic differences in which older patients have shown to be more sensitive to certain toxicities. This includes cardiotoxicity, myelosuppression and neurotoxicity [23,43-46]. The use of complimentary medicines such as high-dose vitamins and herbal supplements is increasing among elderly breast cancer population [47]. Studies have shown that use of complimentary medications alongside chemotherapy have potential to enhance toxic effects of chemotherapy and curtail benefit via CYP metabolism or P-glycoprotein transport [48,49]. However, a more recent study evaluating the association between polypharmacy and chemotherapy-related toxicity and hospitalization failed to show such a relationship [31,50].

Therapeutic drug monitoring is being evaluated in targeted therapies [51]. In breast cancer therapy, tamoxifen drug monitoring has shown potential utility. The efficacy of tamoxifen is dependent on the formation of active metabolites by CYP2D6. The activity of this enzyme is polymorphic with over 100 allelic variants. Large interindividual variability in the metabolite endoxifen has been observed. Studies are underway with lapatinib and pazopanib. There are little age-related changes in these metabolizing enzymes [52]. More clinically relevant is the role of polypharmacy and the potential for drug interactions with CYP2D6. Drug interactions have been reported with antidepressants [53].

1.1 Hormonal therapy

1.1.1 Tamoxifen—Tamoxifen is still used in the treatment of breast cancer in hormonal receptor-positive older women. It is a prodrug which is converted to active metabolites by the CYP system primarily by CYP2D6 [54]. There is a suggestion that the allele may affect treatment outcomes. Although this is not an age-related phenomenon, there is potential of interfering with metabolism through drug interactions and polypharmacy. The activity of the CYP2D6 can be decreased by medicines which inhibit the enzyme resulting in lower levels of the active metabolite endoxifen. Some selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) are inhibitors. Clinicians need to be

cognizant of this interaction and other drugs which may interfere with metabolism. This makes the evaluation of polypharmacy in older patients particularly important and considers stopping unnecessary medications [31,34,35].

1.1.2 Aromatase inhibitors—The aromatase inhibitors are commonly used in post menopausal women with breast cancer. The three available drugs anastrozole, letrozole and exemestane have variable effects on metabolism mediated by P450 [55]. As with tamoxifen, potential for drug interactions need to be carefully monitored as well as evaluation of unnecessary medications. There is a suggestion that the incidence of aromatase inhibitor therapy-related arthralgia may be related to variability in drug metabolism through genetic determinants in the P450 system [56].

1.2 Chemotherapy

1.2.1 Anthracyclines—Anthracyclines such as doxorubicin, epirubicin and PEGylated liposomal doxorubicin (PLD) are among the most active chemotherapeutic agents in breast cancer but their use in elderly is usually limited due to their toxicity profile, with cardiotoxicity being the main concern [57]. In an observational study, it was found that anthracycline-based treatments resulted in significantly higher incidence of congestive heart failure in healthy women between 66 and 70 years of age when compared to non-anthracycline-based regimens. There was no reported difference among the population aged > 70 years [18,58]. The impact of age pharmacokinetics has been studied. In one trial increasing age was associated with decreased clearance of doxorubicin [59]. In another study of doxorubicin/cyclophosphamide, age had no impact on clearance of either drug but there was increased myelosuppression [19]. In an evaluation of epirubicin, variations in clearance may be related to sex and also age in women; however, a wide interpatient variation has been demonstrated [60,61].

Lower doses of anthracycline have been tried in older adults in the adjuvant setting. French American Study Group (FASG) 08 trial compared adjuvant tamoxifen 30 mg/day alone to tamoxifen 30 mg/day combined to weekly epirubicin 30 mg on days 1, 8 and 15 every 28 days for six cycles in patients with breast cancer who were ≥ 65 years of age. In the multivariate analysis, epirubicin significantly reduced the relative risk of relapse (6-year progression-free survival [PFS] 72.6 vs 69.3%, HR: 1.93, $p < 0.005$). There was no difference in overall survival (OS). The toxicities were mild and included grade 2 neutropenia in 5.9%, grade 2 anemia in 2%, grade 3 nausea and vomiting in 4.6% and grade 3 alopecia in 7.2% patients. However, this study was underpowered to conclusively show benefit of low dose anthracycline regimen [62].

In the chemotherapy adjuvant studies for woman at advanced age trial, which was closed early due to slow accrual, 77 patients with endocrine nonresponsive breast cancer were randomized to adjuvant PLD alone versus metronomic doses of CMF versus no chemotherapy. Patients in the PLD group reported worse quality of life, cognitive and physical functioning compared to other groups. After a follow up of 42 months, 19% patients had a breast cancer failure event. Kaplan–Meier estimates of breast cancer failure

events in both PLD and non-PLD arms were comparable (0.78 [95% CI: 0.65 – 0.94]) vs 0.78 [95% CI: 0.68 – 0.93]) [63].

In the metastatic setting, PLD has proven to be efficacious in clinical trials. Biweekly liposomal doxorubicin was tried in 32 patients with metastatic breast cancer who were > 70 years of age. Response rates were 33.3% of 27 evaluable patients and median time to progression was 10.3 months. Grade 3 – 4 toxicities were anemia (6.3%), palmar-plantar erythrodysesthesia (6.3%), mucositis (6.3%), infection (3.1%) and pulmonary embolism (3.1%). No cardiac events were registered [64]. However, another trial showed that PLD for metastatic breast cancer at 40 mg/m^2 every 28 days was poorly tolerated with only 48% of patients completing all six cycles and 3 treatment-related deaths [65]. No age-related changes in pharmacokinetics have been noted, but the toxicity profile of the liposomal compound may be more favorable for older patients as compared to the other anthracyclines such as doxorubicin and epirubicin due to lack of significant cardiac toxicity, alopecia and mucositis.

1.2.2 Taxanes—Paclitaxel is eliminated mainly by hepatic metabolism through CYP3A4 and CYP2C8 activities [66]. Two Cancer and Leukemia Group B (CALGB) studies were used to determine efficacy and tolerability of paclitaxel in the elderly breast cancer population. Patients were divided into three age groups: < 55 (45%), 55 – 64 (29%) and 65 (26%) and higher years of age. It was determined that age had a small effect on paclitaxel pharmacology with decreased clearance; however, but there was little effect on clinically significant toxicities [67]. Patients > 65 years had a shorter time to occurrence of neuropathy [67]. Decreased clearance has been reported in an elderly breast cancer population, but the clinical consequences were not reported [68]. Dose modification based on comorbidity has been evaluated [20].

A *post-hoc* analysis of two studies compared safety and efficacy of weekly paclitaxel, 3 weekly paclitaxel, weekly nab-paclitaxel and weekly docetaxel in MBC in elderly patients [69]. It was found that weekly nab-paclitaxel produced the highest overall response rates of 60 – 64% compared to 3 weekly nab-paclitaxel (22%) and weekly docetaxel (32%). The PFS on weekly nab-paclitaxel was 18.5 months compared to 8.5 – 13.8 months for all other regimens. The incidence of neuropathy with weekly nab-paclitaxel ranged from 17 to 20%, whereas it was 11% in 3 weekly nab-paclitaxel. There were no deaths or severe adverse events [70]. Another evaluation of nab-paclitaxel showed a borderline significant relationship between age and 24-h AUC, but no differences were noted for pharmacodynamic variables (grade 3 toxicity, dose reductions or dose omissions) based on age [69].

The Phase III avastin and docetaxel (AVADO) trial studied the safety and efficacy of docetaxel in combination with bevacizumab in elderly breast cancer patients. Patients with HER2-negative locally recurrent or metastatic breast cancer were treated with docetaxel 100 mg/m^2 plus placebo, bevacizumab 7.5 mg/kg or bevacizumab 15 mg/kg for nine cycles or until unacceptable toxicity or disease progression. The combination of docetaxel and bevacizumab was well tolerated in elderly patients with no excess grade ≥ 3 cardiovascular events. PFS was higher with the combination (HR: 0.63 [95% CI: 0.383 – 1.032] with higher

dose of bevacizumab, HR: 0.76 [95% CI: 0.46 – 1.262] with lower dose of bevacizumab) but OS was not different [71].

The effect of age on the pharmacokinetics of docetaxel has been studied. There are data to support age-related dose reductions due to toxicity differences [72]. In a study of weekly docetaxel, there were no statistically significant age-related changes in pharmacokinetics [72].

1.2.3 Cyclophosphamide, methotrexate, 5-fluorouracil—In a trial evaluating benefit of adjuvant CMF in node-positive postmenopausal patients, it was found that CMF efficacy was low and toxicity was high in patients who were ≥ 65 years of age when compared to their younger counterparts. For the older patients, 5-year disease-free survival (DFS) was 63% with CMF + tamoxifen and 61% with tamoxifen alone (HR: 1, 95% CI: 0.65 – 1.52, p value: 0.99). In the younger group, the corresponding DFS rates were 61 and 53%, respectively (HR: 0.70, 95% CI: 0.53 – 0.91, p value: 0.008). There was greater incidence of grade 3 hematological toxicity (9 vs 5%), grade 3 mucosal toxicity (4 vs 1%) and grade 3 overall toxicity (17 vs 7%) in older age group when compared to younger patients [73].

The elderly breast cancer – docetaxel in adjuvant treatment trial compared adjuvant weekly docetaxel 35 mg/m^2 (days 1, 8, 15) to CMF in elderly (ages 65 – 79 years) early breast cancer patients. Both treatments were given every 4 weeks for four cycles. After 5.5 years of median follow up, weekly docetaxel was not found to be significantly better compared to CMF (HR for DFS: 1.2, 95% CI: 0.82 – 1.75, p = 0.35, HR for death: 1.23, 95% CI: 0.73 – 2.07, p = 0.42). Overall quality of life and toxicities (allergy, fatigue, hair loss, diarrhea, dysgeusia, abdominal pain, neuropathy, cardiac and skin toxicity) were significantly worse with weekly docetaxel [74].

1.2.4 Fluoropyrimidine

1.2.4.1 Capecitabine: There are no age-related changes in pharmacokinetics for capecitabine in patients with normal renal function [75]. In breast cancer patients aged > 75 years, there was decreased absorption demonstration without alteration in relation to elimination as compared to younger patients [76]. It has been shown that patients with renal insufficiency (creatinine clearance < 50 ml/min) have a higher incidence of grade 3 or 4 toxicities [77]. In a prospective study, patients with advanced colorectal cancer aged > 70 years had improved tolerance when doses were adjusted for renal function [78]. In a study comprising elderly Chinese patients, capecitabine monotherapy was compared to combination 5-fluorouracil/epirubicin/cyclophosphamide (FEC) chemotherapy in stage II disease. The 5-year OS rates were 93% in FEC group and 90% in capecitabine group. Quality of life was better in the capecitabine monotherapy group (p < 0.01) [79]. In CALGB 49907, elderly patients with node-positive or high-risk node-negative cancer were stratified by age (65 – 69, 70 – 79, > 80 years) and performance status and randomized to capecitabine alone versus standard adjuvant polychemotherapy for breast cancer, that is, AC or CMF group. Capecitabine was found to be inferior to the standard chemotherapy with higher disease recurrence and death (HR: 2.09, 95% CI: 1.38 – 3.17, p < 0.001) [17]. In the

metastatic setting, single-agent capecitabine has demonstrated efficacy with response rates of 34.9%. However, older populations were unable to tolerate the recommended standard dose of capecitabine which is 1250 mg/m^2. Reduced dose of 1000 mg/m^2 was well tolerated without loss of efficacy [17].

1.2.4.2 5-Fluorouracil: There are no pharmacokinetic data to suggest that doses should be modified based on age alone [80]. There have been age-related changes in toxicity which has been schedule-dependent. Using bolus regimens, older patients had a higher risk of toxicity, including, mucositis, diarrhea, nausea and vomiting [81]. In colorectal cancer, using infusional regimens, there is no change in toxicity or efficacy based on age [82-84].

1.2.5 Vinorelbine—There are some data showing variable pharmacokinetics with age [85,86]. In another study, vinorelbine clearance has shown to be affected by renal and hepatic function but not age [87]. Dose modification should not be made based on age alone. Single-agent vinorelbine has efficacy in treatment of meta-static breast cancer in patients > 60 years of age with response rates of 38%. However, 80% of patients had grade 3 or 4 neutropenia or 70% patients had dose delays after first treatment [88]. Similar results were seen in patients aged > 70 years in first-line treatment of metastatic breast cancer [89].

1.3 Targeted therapy

There are no data to suggest that the metabolism of these drugs is affected by age [90]. Some of the targeted drugs have toxicity issues specific for older patients. Trastuzumab is a humanized mAb targeting the extracellular domain of HER2. Cardiotoxicity is a well-known toxicity. This side effect seems to be dose-dependent and is often reversible. On a retrospective study of patients aged > 65 years, the incidence of congestive heart failure was increased when patients received trastuzumab therapy. Risk factors include age > 80 years, coronary artery disease and hypertension. There was a suggestion that toxicity was schedule-dependent, with the weekly treatment having a higher incidence [91-93]. Everolimus is an inhibitor of the mammalian target of rapamycin. It is used in HER2-negative metastatic disease. The oral bioavailability of everolimus is low (~ 16%) and is moderately bound to plasma proteins (75%). It is metabolized mainly through oxidation by CYP3A4, 3A5 [94]. Toxicities include stomatitis, infection, rash, pneumonitis and hyperglycemia. Older patients had a similar incidence of adverse events but more treatment-related deaths [95]. Pertuzumab and trastuzumab emtansine (T-DM1) have shown efficacy in HER2-positive metastatic breast cancer. Pertuzumab is a mAb which binds to HER2 and inhibits the dimerization of HER2 with other HER receptors. In clinical trials, dual anti-HER2 therapy did not increase the incidence of congestive heart failure [96]. T-DM1 is an antibody–drug conjugate combining trastuzumab and the cytotoxic effect of the microtubule inhibitory agent DM1 [97]. This conjugate has a favorable toxicity profile. Lapatinib is a dual tyrosine kinase inhibitor. The combination of capecitabine and lapatinib was superior to capecitabine alone as first line treatment in patients with untreated brain metastases [98]. Patients > 70 years of age had more grade 3 events. This was particularly significant for increased gastrointestinal toxicity [99].

2. Conclusion

The aging of the population and the resultant increase in the number of older cancer patients necessitates a focus on this group. The changes in the pharmacokinetics and pharmacodynamics with aging in addition to the specific problems associated with an older population need to be recognized and evaluated. Age-related changes in pharmacokinetics and metabolism are rare. The effect of aging is more of the result of comorbidity, particularly renal insufficiency, and polypharmacy with P450 drug interactions. Patients with breast cancer should be given the standard of care and should not be denied appropriate therapy based on age alone. Adjustments in treatment should take into consideration these geriatric factors. Future studies on the metabolism of drug therapy in the older patients need to be undertaken.

3. Expert opinion

Breast cancer is increasingly becoming a disease of the elderly population. However, participation of elderly patients in most therapeutic clinical trials has been low. Although breast cancer in the elderly is biologically less aggressive, ~ 20 – 30% patients have hormone-negative aggressive phenotypes, making chemotherapy an important treatment tool. Elderly patients are at an increased risk of toxicity from chemotherapy because of comorbid conditions and resultant altered drug pharmacokinetics, altered renal and liver function and presence of other factors such as polypharmacy and cognitive decline.

Due to lower representation of the elderly populations in the clinical trials, it is hard to derive firm conclusions regarding benefit of adjuvant chemotherapy in them. However, existing literature suggests that chemotherapy confers a mortality benefit in patients > 65 years of age with hormone-negative or node-positive disease. Risk assessment tools like ADJUVANT online often do not accurately estimate the benefit of chemotherapy in the elderly populations. Therefore, patient selection for adjuvant chemotherapy should be done carefully, keeping in mind age-related factors that could negatively impact the well-being of these patients. Moreover, optimal doses and dosing schedules for adjuvant chemotherapy have not been defined for elderly patients. Although anthracycline-based chemotherapies are preferred adjuvant regimens for aggressive disease in younger patients, anthracycline use on older patients poses a much higher risk of cardiac failure. Non-anthracycline regimens such as CMF may be used but trials show that efficacy is no different than tamoxifen alone in this population. Single-agent capecitabine is inferior when compared to multi-agent adjuvant chemotherapies such as AC and CMF in elderly population.

Several categories of chemotherapeutic agents are effective in metastatic setting including anthracyclines, taxanes, vinca alkaloids, fluoropyrimidine and alkylating agents. Multi-agent chemotherapy is more toxic and should be considered with care. Single-agent sequential chemotherapy is often preferable. There are very little data supporting clinically important variation in pharmacokinetics based on age alone. These changes when present are often not clinically significant and are the result of comorbidity and drug interactions and its effect on P450. The availability of renal function calculations should be utilized for renally excreted drugs. Drug evaluations should investigate polypharmacy and potentially unnecessary

medications which can increase the risk of adverse drug events and toxicity. Geriatric-specific evaluations need to be performed to optimize treatment benefit and safety. It is essential that more elderly patients are encouraged to participate in clinical trials so that we can better assess the impact of chemotherapy.

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Article highlights

- The population is aging with a resultant increase in older breast cancer patients.
- Older patients should not be denied standard of care based on age alone.
- Pharmacokinetic changes based on age alone are not clinically significant; changes are a result of comorbidity particularly renal insufficiency.
- Polypharmacy is an important issue which can affect drug interactions and compliance.
- Drug interactions with CYP450 can be clinically significant.
- Geriatric evaluation should be performed.
- This box summarizes key points contained in the article.