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Adverse Drug Reaction Reporting in Geriatric Oncology in India: An Understudied Topic that Needs Attention

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Abstract

In the elderly, polypharmacy is a common problem, and drug interactions and adverse drug reactions (ADR) have been linked to considerable harm in several population-based studies. However, when compared with other medical disciplines, studies with elderly cancer patients are lacking in oncology and India in particular. Additionally, intake of multiple drugs and, at times, potentially inappropriate medications (PIMs) are also common in older cancer patients. Physiologically, the body's metabolic functions are reduced in the elderly, resulting in altered medication pharmacokinetics and pharmacodynamic characteristics. There is also a high risk of aging-related disorders, and an increase in pharmaceutical use. Because cancer can affect the physiological milieu, patients are more likely to experience negative drug responses, drug–disease interactions, and drug–drug interactions, thereby making the elderly more vulnerable to the ill effects. Considering this, there is a need for greater knowledge and measures that try to lessen exposure to and the risks connected to drug combinations that might be detrimental. As the geriatric population grows, the need to address medical issues among aging cancer patients becomes more pressing, particularly in India. As far as the authors are aware, there is no review that addresses the drug–drug interactions and adverse drug responses brought on by polypharmacy in older cancer patients. It is expected that this endeavor will help the fraternity and the patients, and will serve as a valuable academic material for the health care students.

Keywords
- adverse drug reaction
- drug–drug interaction
- polypharmacy
- geriatric oncology

Introduction

Human life expectancy has increased significantly in recent years due to advances in medical technology and improved living conditions.[1] The World Health Organization (WHO) defines elderly as individuals aged 60 years or older.[2] According to WHO projections, the proportion of the world's population over 60 years old will double from 12% in 2015 to 22% by 2050.[3] In India, 6.6% of the total population is aged ≥65 years.[4] This number is projected to rise to 12.4% by 2026.[5] According to the Technical Group on Population Projections for India and States 2011–2036, the number of

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old people in India increased by almost 34 million in 2021, and will increase by nearly 56 million in 2031.[6] All these projections are predicting that we are entering a period of demographic stagnation marked by an increase in the aging population and by implications that have not been aptly reconnoitered yet.[7]

From a medical standpoint, this graying of the population will be accompanied by a marked increase in geriatric illnesses, which mandate a wholesome understanding of the pathophysiology of aging and appropriate scientifically validated care implement in place.[8] With the growing burden of chronic diseases, polypharmacy, a consequence of multimorbidity, leads to drug–disease and drug–drug interactions. In spite of the fact that medication use and the incidence of adverse drug outcomes both increase with age, the use of drugs by the elderly and their clinical outcomes, particularly adverse drug reactions (ADRs), have not been prominent research topics and continue to be given low priority, at least in developing countries like India.[9] This needs precedence as ADRs result in hospital readmission or prolongation of hospital stay, thereby increasing the direct and indirect costs of treatment. Likewise, data on ADRs in older patients with cancer are meager.[10,11] Many of the anticancer pharmacovigilance studies available do not provide age-specific delineation of events.[12] Because of the scarcity of data on adverse effects in genetically diverse Indian population, robust pharmacovigilance is required, especially in older population.[13] According to the findings of a research on ADR monitoring in elderly patients at a rural teaching hospital, the proportion of ADRs recorded in those over the age of 75 is lower (6.18%), and the prevalence of ADRs decreases as one gets older.[11] Another study conducted over 3 years with 1,328 patients found that the majority of ADRs (30.18%) occurred in the age groups of 40 to 49 years and 50 to 59 years (26.56%), and ADRs in the age groups of 60 to 69, 70 to 79, and $\geq$80 years were 13.06, 7.76, and 1.76%, respectively.[14] In another study, ADRs in patients aged 65 to 69 years were 39.17%, 60 to 64 years were 29.89%, 70 to 74 years were 24.74%, and above 75 years were 6%.[11] One explanation for this could be the lower proclivity of older patients for seeking medical care and reporting of ADRs.

With the surge of novel anticancer medications entering the market, an active monitoring system is required to better understand these drugs and their side effects. The implementation of an active pharmacovigilance program is essential for the early detection of unrecognized adverse responses, understanding the trends of known adverse reactions, identifying risk factors, and the disseminating information.[12] Moreover, focused pharmacovigilance studies are required in the older age group to bridge the gap in existing evidence.

ADR in Oncology

Oncology patients have a high rate of ADRs since chemotherapy is very complicated and cytotoxic, and cancer patients have low tolerance. ADRs in chemotherapy patients are also increased by polypharmacy and multimorbidity. Antineoplastic agents were the most prevalent class of medications producing ADRs, accounting for 21.8% of reported ADRs in South India.[15] Thus, recognizing ADR patterns with anticancer medications is critical to improving patient quality of life and lowering ADR-related hospitalization costs.

Vulnerability to Adverse Drug Reactions

In a 2-year prospective analysis of 4,005 Indian ambulatory aged individuals, ADRs were linked to older age (odds ratio [OR] = 1.7), polypharmacy (OR = 1.8), longer treatment duration (OR = 2.28), and multiple diagnoses (OR = 1.8).[16] Approximately 69% of the patients were treated for two or more illnesses.[16] The average number and duration of medications prescribed were 6.45 ± 0.04 and 36.25 ± 0.42 days, respectively.[16] ADRs increase with age, and are twice as prevalent among people older than 65 years.[17] Among older cancer patients, a strong connection was observed with increasing age (OR = 2.22; 95% confidence interval [CI]: 1.698–2.909) and overweight (OR = 16.68; 95% CI: 2.179–127.741).[17] Patients older than 80 years were at significant risk of ADRs compared with the patients of in the 60- to 69-year age group.[16] In a study, ADRs were seen in 58.6% of geriatric patients. Another study found that only 16.43% of older people had ADRs.[18] The age distribution revealed that most (41.4%) were in the 60- to 65-year age range, followed by 66 to 70 (40.8), 71 to 75 (13.2), and 76 to 80 (4.6%) year age groups.[19]

There was no difference in the incidence of ADRs between female and male patients (OR = 1.09; CI = 0.88–1.28).[16] On the contrary, in studies by Harugeri et al (OR = 1.52; CI: 1.04–2.22; $p = 0.03$), Raut et al (55.48%), and Prathyusha et al, female sex was shown to be an important ADR risk factor.[20–22] In a study by Sharma et al on chemotherapy-induced ADRs, females predominated ($n = 88$, 54%), with only 16% of ADRs occurring in those older than 65 years.[23] It could be attributed to a higher body fat percentage and a lower body water content in females than in men, which can affect the distribution and elimination of drugs in the body. The risk increases with age and polypharmacy.[24] Contrary to these studies, males had more ADRs compared with females in a study by Pauldurai et al, which could be explained by a higher male proportion in the study (65.76 vs. 34.23%).[11] In a study by Mallik et al, ADRs were found to be significantly more prevalent in male patients and those between the ages of 61 and 70 years.[25]

Extent of ADR in Elderly

In general, ADR-related hospital admissions accounted for 5.9 to 10% of all admissions.[20,21,26] An ADR-related hospitalization accounted for 0.7% of all hospitalizations in one South Indian study in the general population, and ADR-related mortality accounted for 1.8% of all hospitalizations.[27] In a study of older patients admitted to the medical emergency department, 14.4% were drug related, 6.7% were due to ADRs, and 7.6% were due to prescription noncompliance.[28]

Reports suggest that there is a fourfold increase in the likelihood of ADR-related hospitalization for the elderly

compared with the younger population (16.6 vs. 4.1%).[29] ADRs were detected in 18.6% of geriatric patients by Pauldurai et al.[11] It is higher than the 3 to 6% rate reported in the general population and United Kingdom geriatric patients (14.7%), but less than those in the United States and Europe (20%).[11,30] Eighty-eight percent of ADR-related hospitalizations in the elderly are avoidable, compared with 24% of ADR-related hospitalizations in the general population.[29] Two-thirds of senior patients with ADR (68.42%) required hospitalization for treatment. One-fifth of patients (19.29%) required immediate intensive care unit (ICU) admission or suffered irreversible disability or death.[11] The entire cost of a hospital stay caused by ADRs was US$4,350 (INR 200,100), which translates to US$80.5 per patient.[20] Another study showed the average cost of treating an ADR among hospitalized inpatients in India was Rs.1,328.71 (US$21.90).[21]

The Nature of ADRs in Older People

More than 80% of ADRs that result in hospitalization are predictable, dose-dependent type A responses. Drugs with a low therapeutic index are more likely to cause type A responses, and this is especially true among the elderly.[31] Type B ADRs are thought to be unpredictable and dose independent. They are not frequent, but when they do occur, they may be life-threatening.

Risk Factors for ADRs in the Elderly

Older people have distinct pharmacokinetic characteristics, multimorbidity, and polypharmacy, making them more susceptible to adverse medication responses. To reduce the risk of ADRs, health care professionals must be aware of these risk factors and closely monitor the medications of elderly patients to minimize the risk of ADRs.

Age: Cancer rates rise with age, and around 60% of all malignancies and 70% of cancer deaths occur in those older than 65 years.[32] There has been much dispute about whether age is an independent risk factor for ADRs or just a marker for comorbidities and changed pharmacokinetics. The interindividual heterogeneity of the aging process indicates a significantly more complicated clinical reality. Patient-specific physiological and functional factors are probably more prognostic of outcomes associated with specific pharmacological regimens than age.[33]

Pharmacokinetics: Individuals older than 65 years have varying levels of health, impairment, and physiologic reserves; hence, applying available standard chronic illness guidelines for older adults are insufficient. Because the clinical studies on which the recommendations are based strictly excluded older patients, extrapolating these suggestions to older patients is erroneous.[34] Drug toxicity and ADRs are increased with age due to physiological changes that impact pharmacokinetics such as absorption, volume of drug distribution, metabolism, and excretion.

Absorption: In the gastrointestinal system, several changes occur, including decreased salivary flow, decreased stomach acid output, increased gastric emptying time, decreased gastrointestinal motility, decreased absorptive capacity of intestinal cells, and reduced splanchnic blood flow. However, despite these modifications, there is a minimal difference in medication absorption with age.[35]

Metabolism: In healthy aging, a drop in liver size by 25 to 35% and a decrease in hepatic blood flow of more than 40% are seen, both of which result in decreased drug clearance. As a result of decreased first-pass metabolism and enhanced bioavailability, there are elevated serum levels for drugs with a high hepatic extraction, which leads to detrimental consequences in patients taking these medications.[36]

Distribution: Water-soluble drugs have greater serum concentrations due to the reduction in total body water with age. Similarly, the half-life of fat-soluble vitamins increases due to the high body fat proportion seen with aging. Acidic drugs (diazepam, phenytoin, and warfarin) attach to albumin, whereas basic drugs (lignocaine, propranolol) bind to α-1 glycoprotein. Albumin is typically decreased in malnutrition or severe sickness, but α-1 acid glycoprotein is usually raised. Since the fundamental predictor of drug activity is free plasma concentration, the effects of protein binding on free plasma concentration are quickly counterbalanced by increases in clearance.[35]

Elimination: Kidney mass and blood flow diminish, resulting in a 40% loss in available nephrons by the eighth decade. Chronic diseases, including hypertension and heart failure, have a substantial impact on glomerular filtration rate (GFR).[36] Moreover, renal function declines with age, affecting medication clearance, which leads to the drug's toxicity. As part of "In the Renal Insufficiency and Anticancer Medications" (IRMA) trial, 50 to 60% of elderly cancer patients had impaired renal function, and 80% were treated with anticancer medicines that either required dose modification for renal insufficiency or were potentially nephrotoxic.[37] Patients with impaired renal function are at risk of major side effects from narrow therapeutic index drugs, especially anticancer drugs.

Multimorbidity: It is well acknowledged that treating patients who have multiple chronic medical illnesses is a difficult task for health care providers.[38,39] More than 40% of the population (all ages included) in the United Kingdom had at least one long-term ailment, with ∼25% of the whole population having more than one long-term illness.[40] In Spain, 67.5% of the elderly population suffered from two or more chronic diseases, and multimorbidity was found in 32.2% of males and 45.3% of females.[41] Recent research has also shown that multimorbidity is prevalent in low- and middle-income Asian nations.[42]

About a third of elderly in India have multiple diseases. The most common are hypertension, gastrointestinal (GI) illnesses, musculoskeletal disorders, diabetes, and skin diseases.[43] National Family Health Survey data from 2015 to 2016 revealed that 1.6% of women in India had multimorbidity, with a greater frequency among women from the southern part of the India.[44] The frequency of multimorbidity rises significantly with age. The incidence of multimorbidity is significant (48.8%) among the rural old population in eastern India, particularly among those living in rural

areas.[38] Multimorbidity was found to be highest in adults aged ≥60 years (37%), who consumed alcohol (12.3%), had a body mass index of 25 kg/m^2 (14.1%), had an excessive waist circumference (17.1%), and had a history of chronic conditions in their families (12.4%).[45] The most prevalent dyads (two chronic disorders) were found in 25% of the patients, followed by triads (15.2%) and four or more chronic diseases in 8.7% of the patients.[38] Comorbidities were present in 51.3% of geriatric oncology patients who participated in one study.[19]

Gender is also a well-recognized factor in multimorbidity. In women, cardiovascular and metabolic problems have been shown to be less common; however, psychogeriatric diseases have been found to be more common.[41] As a result of polypharmacy and complicated treatment regimens, patients with multimorbidity are at greater risk of adverse drug events and poor medication adherence. Poor health, old age, cognitive impairment, inadequate health literacy, and the presence of depression or anxiety as a comorbid condition all obscure the likelihood of receiving coordinated, effective health care delivery.[46]

Polypharmacy: As the number of ailments rises, so does the number of prescriptions written for them. There is an increased risk of medication interactions and adverse effects due to polypharmacy.[36] Antineoplastics, antibiotics, anticoagulants, digoxin, diuretics, hypoglycemics, and nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed medications for the elderly.[31] Polypharmacy is responsible for 60% of ADRs that result in hospitalization and 70% of ADRs that occur during hospitalization.[31] It is uncertain if polypharmacy and PIM usage only serve as markers for a sicker patient with a poorer outcome, who needs more prescriptions or if there is a correlation between these factors.[47]

Several small studies have shown that multiple drugs are prescribed to treat comorbid illnesses and to avoid disease in elderly patients. In a south Indian study, 56.53% of elderly patients were given six to eight medications.[11] In a British study on elderly cancer patients, the median daily medications were seven (interquartile range [IQR]: 1–17).[48] A Canadian study on newly diagnosed cancer patients revealed that at least five medicines were administered before systemic anticancer treatment.[49] An Irish study found that elderly patients were given more drugs than younger patients (median: 7 [IQR: 4–9] vs. 4 [IQR: 2–7]; $p = 0.001$).[30] This number was lower in an Indian study (5 [IQR: 2–8]).[47] In a geriatric study from Turkey, PIMs were present in only 26.6%of the patients ($p < 0.001$),[50] while, four of five elderly Indian cancer patients in our study were on a PIM.[47] In this study, polypharmacy was found to be at its highest level in 70% ($p = 0.001$) of patients with lung cancer, followed by 52% of patients with genitourinary primary cancers, 45% with GI cancers, and 40% with head and neck cancers.[47] In 80% of patients who were on PIMs, proton pump inhibitors (PPI; 33%)and tramadol (30%) were the most often received PIMs. Unindicated drugs were used by 20% of patients, including multivitamin/iron supplements (17%), calcium (3%), and statins (2%).[47] This is a concerning statistic, and increasing awareness of polypharmacy and PIM usage would be a good start. To guarantee safe drug prescription practices in older cancer patients, it is crucial to recognize the issue, exercise caution while prescribing multiple drugs for comorbidities, and replace them with less toxic, more age-appropriate treat regimens.

Over-the-counter (OTC) or complementary and alternative medicines (CAM): Due to multimorbidity, elderly people are more likely to use OTC or nonprescription medications. Due to widespread trust and confidence in traditional remedies and easy access to numerous OTC pharmaceuticals, CAM is becoming more important among older patients. Complementary or herbal remedies may cause or contribute to drug interactions and ADRs, especially in an older population. Since the elderly are at greater risk of adverse drug events and drug interactions, knowing their medication habits is essential.[51] CAM was used by 59% of patients between the ages of 60 and 69 years, compared with 76% of patients beyond the age of 70 years.[51] CAM was the initial choice of therapy for 65.7% of the users in North India.[51] In studies done in Tamil Nadu and North India, the prevalence of the usage of OTC drugs among the elderly population was found to be 51 and 65.5%, respectively, which is higher compared with an Australian study (17.7–35.5%).[51–53] In two other Indian studies, CAM was reported to be used by 23% of oncology patients.[47,54] Sixty-nine percent of those polled said they used CAM in addition to modern medicine.[54] Gender, education, rural or urban background, or distance from a modern medicine system health care facility had no effect on CAM practice in the elderly.[51] On the other hand, higher socioeconomic status ($p = 0.015$) and literacy rates were associated with OTC drug use ($p = 0.003$) in another study that is similar to western studies.[53,55,56]

Ayurveda is the most popular CAM (64.8%), followed by homeopathy (62.4%) with many patients using both practices together.[51] Due to a lack of elderly patients reporting their use of CAM, preventing CAM-related side effects and drug interactions is difficult. Most people feel that CAM is safe and that they are more satisfied with it. As a result of these beliefs, the elderly are reluctant to disclose their use of CAM to their health care practitioners. Fifty-seven percent of patients believed CAM was safe with regular treatment.[51] Modern doctors did not probe 91.5% of elderly patients about CAM use, and 85.5% of patients did not disclose such information until prompted.[51]

The likelihood of drug interactions rises as the number of drugs increases. Nearly a third of patients in a Canadian study were found to be at risk of an herb–drug interaction.[57] A study has shown that 19.2% of warfarin patients were also taking a CAM that might interact with it.[58] Anticoagulants such as ginkgo biloba, garlic, and fish oils should be used with caution in elderly people who are taking warfarin, aspirin, or clopidogrel.

In parallel, many studies have shown that CAM is beneficial in alleviating the effects of cancer and the side effects of cancer therapy.[59–61] In recent years, there has been a mounting interest from academic and commercial researchers in the use of herbal remedies for the treatment and prevention

of cancer. But how much of these spices is consumed on a daily basis determines whether they have positive or negative effects. Even though the synergistic or additive combinations of either herbs alone or in conjunction with chemotherapeutic medicines have shown a diverse range of benefits, the creation of an effective combination is always challenging. Furthermore, many CAM practitioners still maintain the confidentiality of the exact ingredients in their blends. To optimally utilize CAM in chemotherapy, further explorations are required with different combinations to confirm their effectiveness, compatibility, and ideal dose. As a result, CAM use in cancer patients should be discouraged until valid scientific data are available.

Patient-related errors and noncompliance: Patient-related medication errors were most often caused by automatism, disregard for physician guidance, and self-modification of medicine. Complex drug regimens, cognitive disability, compromised mental acuities, poor eyesight, and poor physical dexterity are all common in error-prone patients. Poor medication memory, multiple physicians, female sex, polypharmacy, drug costs, and nonconventional therapy were related to an increased risk of hospitalization due to noncompliance.[28]

Strategies to Prevent ADRs in Elderly

To meet the growing number of older cancer patients, treatment strategies need improvement.[62] Patients' life expectancy, functional reserve, social support, and personal preferences should all be considered while developing treatment paradigms, and the treatment should be individualized for optimal outcomes.[62] In a nutshell, the care of older patients should be approached from a holistic standpoint.

There are several tools commonly used for geriatric assessments, including the following: the Mini-Mental State Examination (MMSE), a brief test that assesses cognitive function, including memory, attention, and language abilities; Geriatric Depression Scale (GDS), a questionnaire that assesses for signs of depression in older adults; Barthel Index, a measure of functional independence that assesses activities of daily living such as bathing, dressing, and toileting; Instrumental Activities of Daily Living (IADL) Scale, an assessment tool that measures a person's ability to perform tasks related to living independently, such as managing finances and using the telephone; Geriatric Assessment (GA), a comprehensive multidimensional assessment that includes evaluation of an older person's functional status, medical conditions, cognitive status, emotional well-being, nutrition, and social support systems.

A Comprehensive Geriatric Assessment (CGA) is a good way to determine life expectancy and treatment tolerance, as well as identify reversible factors that may interfere with cancer therapy, such as depression, malnutrition, anemia, neutropenia, and caregiver support.[62] Another brief assessment is the Mini-Comprehensive Geriatric Assessment (Mini-CGA), which aims to identify and address the multiple health and functional needs of older adults in a timely and efficient manner. It typically includes a focused assessment of the patient's medical, functional, and psychosocial status, as well as a review of medications and potential drug-related problems and referrals for additional specialty evaluations as needed.[63]

Regular medication safety monitoring aids in the identification of the most prevalent ADRs and their underlying causes in cancer patients. During the commencement and continuation of anticancer therapy, all anticancer agents must be monitored for safety. Spontaneous reporting and active surveillance techniques are useful in this aspect. To balance the need and avoid polypharmacy, vital drugs must be monitored for underuse. Patients need to be educated about important side effects and what to do if they occur.

People with multimorbidity may require medical assistance on an episodic basis, and the only way to meet their overall health care demands is by improving the health care system. Brown bag reviews, in which patients are required to bring all of their drugs, including OTC and alternative treatments, are common in the United States and may be replicated here.[36] Considering this, medication reconciliation, a strategy used to discover inconsistencies in drug regimens, is especially crucial during transitions in care, when prescription mistakes are common.[64]

The development of systems for improved communication and coordination at multiple levels of the health care system, and the improvement of support for integrated care across the primary and secondary, health and social care sectors needs focus. Artificial intelligence (AI) based systems that have the potential to alert clinicians to possible drug interactions or errors display relevant guidelines, suggest dosing and frequency, and possible alternative medications can significantly improve prescriptions.[65] AI also has the ability to guide clinical decision-making in real time to decrease the incidence, length, and severity of ADRs. Before prescribing drugs, AI could give fast and reliable predictions of which patients were likely to get ADRs. Avoiding reliance on single-condition clinical guidelines that fail to account for people with multiple conditions, as well as simplifying treatment regimens, advocating for appropriate polypharmacy, and using medication aids to promote adherence, are all beneficial for preventing drug interactions and ADRs in the elderly.[46]

Conclusion

ADRs are very common in older patients with cancer due to pharmacokinetic alterations, multimorbidity, polypharmacy, and nonadherence. There is a disparity in age and gender proportions in reporting ADRs. ADRs are underreported in elderly patients. Active surveillance systems, in addition to spontaneous reporting, may be more effective for evaluating medication safety in cancer patients. Hence, studies focusing on pharmacovigilance in older patients are the need of the hour.

Conflict of Interest
None declared.

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