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CHEMOTHERAPY IN THE ELDERLY

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Abstract

The number of elderly patients with malignancy is growing and is likely to have a major impact on resources, quality of care, health economics and treatment options. Decisions regarding treatment options with chemotherapy are limited by the scarcity of data specifically addressing the issues regarding chemotherapy in the elderly. The problem is further confounded by issues such as co-morbidity, poly-pharmacy, cognitive impairments, emotional problems, functional limitations, sensory impairment and a lack of social support. Ageing is associated with specific physiologic changes in functional status, organ function and drug pharmacokinetics. Optimising cancer care and chemotherapy delivery in the elderly requires a better understanding of the specific pharmacokinetic and pharmacodynamic issues and administration of chemotherapy in this age group. Elderly participation in clinical trials and specific research is essential to guide treatment decisions and further research is required to provide evidence-based models to guide treatment decisions. In an Australian setting, the development of a geriatric oncology specific group as a means of facilitating collaboration with geriatricians, development of specific elderly research programs and clinical trials, education and development of treatment guidelines would further improve outcomes of our elderly patients undergoing cancer treatment.

Magnitude of the problem

Cancer is a disease that mostly affects older individuals, with approximately 60% of cancer morbidity and 70% of cancer mortality occurring in patients over 65 years of age.^{1,2} This age group is growing rapidly: in Australia in 2003, there were 3.35 million people aged 60 years and over (17% of the population), compared to three million people (16%) in 1998. It is expected these numbers will increase steadily. In 2002, median life expectancy at age 65 years was 17.3 years for males and 20.8 years for females. Since 1982, at 65 years of age males have gained 3.7 years of life expectancy and females three years. In 2003, just over half had a reported disability (51%) and 19% had a profound or severe core-activity limitation.³ People aged 85 years and over reported a much higher need for assistance than those aged 60-69 years (84% compared with 26%).⁴

Ageing is an important part of human development and it is influenced by the biological changes that occur, but also reflects cultural and societal conventions. Specific strategies to address these problems need to be developed as a priority. Elderly cancer patients often present with medical and physiologic problems that make the selection of their optimal treatment challenging. The problem is further confounded by issues such as co-morbidity, poly-pharmacy, cognitive impairments, emotional problems, functional limitations, sensory impairment and a lack of social support.

Until recently, almost all clinical cancer research under represented elderly patients.⁵⁻⁸ Most of the published trials in oncology have used chronological age limits to define cancer patients as elderly; 65 or 70 and less often 80 years of age are commonly used limits for patients with solid tumours. Data from these trials have been extrapolated to guide treatment decisions in the elderly population. Despite these limitations, physicians attempt to tailor chemotherapeutic treatments for this

population of patients that limit exposure to potentially futile or unjustifiably toxic treatments, while not denying them beneficial treatments which may impact on survival, symptoms and quality of life. This is further complicated by the diversity and heterogeneity of this population. At present, there are few evidence-based guidelines or trials to assist in this regard.

Under-treatment of elderly cancer patients with dose reduction of adjuvant chemotherapy or total therapeutic abstinence is not unusual in practice. Under-utilisation of resources might also include access to palliative care, treatment of pain, surgical reconstruction and rehabilitation. Common justification for under-treatment includes co-existing medical problems, chronological age, lack or scarcity of data for that age group, lack of relevant clinical trials and increased risk of adverse events.

In current practice, the elderly are often excluded from participation in clinical trials and receive untested or inadequate treatment based on unvalidated criteria. Elderly specific clinical trials are an essential requirement to guide clinicians more appropriately to optimise chemotherapy delivery to this specific population. Studies incorporating the pharmacodynamic and the pharmacokinetic effects on ageing are necessary. This paper will address issues related to chemotherapy delivery in the elderly.

Impact on the pharmacokinetics and pharmacodynamics

Ageing is associated with physiologic changes in functional status, organ function and drug pharmacokinetics. Physiologic reserve decreases progressively with ageing.^{9,10} Organ specific age related physiologic decline begins in the third decade of life. It is not evident at times of rest but becomes most apparent when the body is stressed.¹¹ Both cancer and its treatment can be considered as physiologic stressors

and the age related decrease in physiologic reserve can affect tolerance to cancer treatment.

Ageing is associated with decreases in marrow reserve, drug clearance and lean body mass. Furthermore, concomitant co-morbidities that affect functional status, general health and tumour symptoms are frequently present in this patient population. Co-morbidities in older patients can strongly affect the risk and behaviour of cancer and their related treatment. This effect is associated with syndromes with common patho-physiologic mechanisms, such as diabetes mellitus, the metabolic disorders and inflammatory diseases.¹²⁻¹⁵

The levels of a number of inflammatory cytokines have been found to be elevated in common cognitive disorders of ageing.¹⁶ The circulating level of Interleukin-6 is elevated in most geriatric syndromes and often reflects compromised muscular function.¹⁷ The circulating level of C-reactive protein, another inflammatory marker, predicts increased risk of cardiovascular mortality.¹⁸ Non-specific markers of autoimmunity, such as antinuclear antibodies, also tend to increase with age.

A number of age related changes in drug absorption, distribution, metabolism and excretion with ageing can contribute to differences in treatment tolerance between older and younger patients. An increased toxicity in elderly patients with cancer may be due to increased exposure to a drug either by prolonged half-life, due to decreased elimination, or by impaired renal function and also changes in pharmacodynamics caused by increased vulnerability of organs with age. The volume of distribution changes; total body water is reduced to about 50% (instead of 60%), whereas total body fat increases. Other factors associated with a change of distribution are binding of drugs to erythrocytes (eg. anthracyclines, epipodophyllotoxins and oxaliplatin) and proteins (especially albumin). Thus, hypoproteinemia and anaemia can alter drug distribution. The absorption of drugs can be affected by decreased gastrointestinal motility, decreased splanchnic blood flow, decreased secretion of digestive enzymes and mucosal atrophy.¹⁹⁻²⁰ However, to date no unfavourable data for orally applied cytotoxic drugs due to a decreased absorption have been reported in elderly patients.

With the increased use of oral therapy, drug compliance is an important issue.²¹ The increase in body fat leads to a rise in the volume of distribution for lipid soluble drugs and a diminution in the volume of distribution for hydrophilic drugs. In the cancer population, malnutrition and hypoalbuminaemia can result in an increased unbound concentration of drugs that are albumin-bound.²² Hepatic mass and blood flow decrease with age.^{9,23} The impact of the decline in hepatic mass and blood flow on hepatic enzyme function is controversial.²⁴⁻²⁶

Changes in renal function are less controversial. The decline in Glomerular Filtration Rate (GFR) with age is estimated at 0.75 mL/min per year after age 40; however, approximately one third of patients have no change in creatinine clearance with age.²⁷ This reduced renal function does not usually result in increased serum creatinine levels because of the simultaneous loss of muscle mass.²⁸ Therefore, serum creatinine is not an

adequate indicator of renal function in the older patient. All formulas used to calculate renal function have been primarily validated in a younger group of patients without renal disease and are not as accurate in older patients.^{29,30} The accuracy of the Cockcroft-Gault, Jelliffe and Wright formulas in a population of older patients with cancer has been evaluated and the Wright formula was the most accurate formula to calculate GFR; however, the majority of patients in this study had a GFR >50 mL/min.³¹

The decline in GFR with age translates into pharmacokinetic alterations of drugs or their active metabolites which are excreted by the kidneys. Prudence with adjusting doses of renally excreted drugs to prevent toxicity cannot be overemphasised.

Polypharmacy, which is common in the elderly, increases the risk of adverse events.³²⁻³⁴ The older patient with cancer is particularly at risk for adverse drug events due to issues relating to polypharmacy. Agents such as supportive care medications (anticholinergics, benzodiazepines, dexamethasone) may have exaggerated effects in an older person.^{33,34} In addition, clearance of chemotherapeutic agents may be affected by concomitant drugs, which can lead to decreased clearance of the chemotherapy (placing the patient at increased risk of toxicity) or increased clearance (placing the patient at risk of ineffective therapy).

Many older patients are on common drugs causing cytochrome P450 related interactions, including selective serotonin reuptake inhibitors, phenytoin, steroids, ketoconazole and macrolide antibiotics. These patients may experience important drug interactions which involve antineoplastic agents such as ifosfamide, vinca alkaloids, etoposide, taxanes and aromatase inhibitors.²⁴

Strategies to minimise the risk for drug-to-drug interactions involve: a thorough medication history including prescribed medications, over-the-counter medications and herbal medicines at each visit, becoming familiar with the lists of drugs that should be avoided in older patients; eliminating any unnecessary medications; and paying attention to patient adherence to prescribed medications.^{33,35} Moreover, it is essential to realise that elderly patients often have more than one clinician prescribing different medications without adequate communication among them.

Older patients are at increased risk of myelosuppression and toxicity resulting from age-related decline in organ function.³⁶ Haematological toxicity is more common in elderly patients. Chemotherapy is associated with a higher rate of infection, more hospitalisations and a higher mortality in older age groups.³⁶ Furthermore, the increased use of haematopoietic growth factors has led to a shift in the toxicity profile. The dose-limiting toxicity of many regimens has shifted to non-haematological toxicity, particularly neuropathy and gastrointestinal toxicity, which remain significant problems for older patients.

It is important to appreciate the limitations of the data on chemotherapy in the elderly available at present. Few studies have looked specifically at the older patient

group, with most analysing a subpopulation of older participants within larger studies, limiting the numbers, validity and reliability. Additional studies of pharmacokinetics of cancer therapies in the older patient are needed, based on the data to date, it is likely that more factors in addition to pharmacokinetics and chronologic age may be significant predictors of tolerance to chemotherapy. Future pharmacokinetic studies in older patients should include a thorough evaluation of physiologic factors, such as baseline renal function, hepatic function, haemoglobin and albumin levels. In addition, studies should include an assessment of factors apart from chronologic age that independently predict morbidity and mortality in the geriatric population, including all aspects of functional status, cognitive state, comorbid illnesses, nutritional state and psychological status.³⁷⁻³⁸ Studies that include these parameters may provide insights into the factors contributing to tolerability of chemotherapy and lead to interventions to improve treatment tolerance.

Chemotherapy agents and the data

Although it is beyond the scope of this article, we will briefly discuss a few aspects of specific chemotherapeutic agents commonly used in clinical practice. In elderly breast cancer patients treated with doxorubicin and cyclophosphamide there is evidence of an age-related decrease in absolute neutrophil nadir count. However, Dees et al concluded that healthy older patients should not be denied adjuvant chemotherapy on the basis of age alone.³⁹ There is no reproducible evidence for systematic dose reduction of cyclophosphamide based on age alone, particularly in the adjuvant setting.

Cisplatin is utilised in the treatment of numerous malignancies. The clearance is primarily dependent on renal function. The potential nephrotoxicity of cisplatin is a concern, but toxicity in the elderly can be minimised with appropriate safety measures, particularly with intravenous hydration.⁴⁰⁻⁴¹ Carboplatin, which has a mechanism of action similar to cisplatin, is primarily excreted renally while the remainder binds to tissue proteins and is inactivated.⁴² Dosing using creatinine clearances derived from formulae have limitations, particularly in elderly patients. Retrospective studies have attempted to quantify the reliability and the accuracy of these methods in a particular elderly cancer patient group.³¹

Fluoropyrimidines such as fluorouracil and capecitabine are widely used agents in solid malignancies in the geriatric population. They are often arbitrarily reduced in dosage.⁴³⁻⁴⁵ The pharmacokinetics of capecitabine for instance is not affected by age in patients with normal renal function.⁴⁶ There is no pharmacokinetic basis for dose modification based on age alone.⁴⁷ However, there may be significant age-related toxicities. An overview of seven phase III trials involving fluorouracil with either leucovorin or levamisole showed that no interaction between age and outcome could be identified. However, age older than 70 years correlated with a higher occurrence of treatment-related leucopaenia of borderline significance.⁴⁸ A retrospective analysis of European trials has showed that fit elderly patients

experience equivalent benefits and toxicities as younger patients.⁴⁹

With regard to taxanes, several phase II trials have concluded that the pharmacokinetic analysis of differences in age related clearance of this agent were negligible compared with the interpatient variability in drug metabolism.⁵⁰

Conclusions

Optimising cancer care and chemotherapy delivery in the elderly requires a better understanding of the specific pharmacokinetic and pharmacodynamic issues and administration of chemotherapy in this age group. Utilising a comprehensive geriatric assessment that incorporates aspects such as polypharmacy, comorbidities and social issues will be of great assistance. Outcomes of such an assessment tool may influence chemotherapy delivery, toxicity and prognosis. Further research is required to provide evidence-based models to guide treatment decisions.

There are great opportunities for research and development of scientific, evidence-based guidelines for geriatric oncology practice. There is an increasing demand for elderly specific cancer research. In an Australian setting, the development of a geriatric oncology specific group as a means of facilitating collaboration with geriatricians, development of specific elderly research programs and clinical trials, education and development of treatment guidelines, would further improve outcomes of our elderly patients undergoing cancer treatment.

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