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Tolerability of Chemotherapy in Elderly Patients

Martin Hohenegger

Abstract: In Western countries, prolonged life expectancies increase the importance of geriatric oncology. Consequently, the rationale for an aggressive procedure or best supportive care is a complex evaluation process which has to summarize the global situation of the old patient. While clinical cancer studies are designed on the basis of tumour type, staging, and other factors, factors such age, expected lifetime, performance status, and assessment of elderly patients are neglected. For instance, comorbidities > 75 years are found in almost 80 % for a single chronic disease, while \geq 3 diagnoses are detectable in $\frac{1}{3}$. Thus, it should be the primary aim to balance treatment, side effects, and potential benefits with reasonable therapeutic goals.

While conventional chemotherapy was limited in elderly people by serious life-threatening side effects, novel individualized drug regimens may support compliance and improve therapeutic success. The introduction of novel targeted therapies currently roughens up the field of oncology. However, consequences of the new possible drug combinations in the light of side effects are pending. Particularly in elderly patients, the tolerability of these new concepts requires more evidencebased data, nevertheless, first data on adverse event comparisons are encouraging.

The concept of a comprehensive geriatric assessment has been suggested to evaluate the multidimensional aspects of elderly cancer patients. Thus, profiling the personalized therapy may involve targeted anti-cancer therapy and adapted pharmacokinetics to ensure best clinical outcome. This review will summarize critical pharmacokinetic parameters which are important also in the general pharmacotherapy of elderly people. **Eur Assoc Neurooncol Mag 2011; 1 (1): 21–4.**

Key words: elderly, cancer, renal function, dose adjustment

Introduction

By definition, geriatricians assume now an age > 75 years as the landmark for old age. One can speculate that improvement of overall therapeutic concepts may elevate this threshold into the eighties. Nevertheless, the increase in length of life expectancy is accompanied by diseases and impaired mobility as monitored between 1998 and 2008 in the United States [1]. A central issue in clinical trials including elderly patients is given by the selection bias in favour of treatment. Inclusion criteria support selection of individuals who are considered fit enough to survive the study period. Thus, overall survival may not represent an appropriate endpoint in particular in the oldest age group. Nevertheless, age-stratified analyses in clinical trials may elucidate categories of benefit and harm in these age groups. Consequently, overall outcome and, even more importantly, quality of life aspects are important for elderly people, in particular in the presence of malignancies. Hence, adaption of chemotherapy to age-specific situations and disease parameters may reduce risk of adverse events and interactions from polypharmacy.

Pharmacological cancer therapy in elderly people has to account for pharmacokinetic and -dynamic aspects in view of age-related changes in organ function and disease-related alterations. Age-related changes in organ function might still be physiological and have to be discriminated from disease-related malfunction of organs.

Physiological Changes with Age

Age-related changes in organ functions generally do not result in reduced organ function at rest. However, adaption of organ function is reduced in response to physical activity, stress, or disease-related stress situations and correlates with age. Eg, while lung function in healthy old individuals is not impaired under rest, there is a delayed and diminished response to hypoxia and hypercapnia in the elderly [2, 3]. Similarly, the cardiovascular response to exercise progressively declines with age [4, 5].

Only a limited number of clinical studies are available monitoring the pharmacokinetics of anti-cancer therapeutics in the elderly. In general, a prolongation of the drug half-lives is observed and attributed to a reduction in renal function. This is an oversimplification which does not account for the multiple organic changes due to aging.

Age-related changes in the gastrointestinal tract involve reduction in splanchnic blood flow, motility, and secretory gland activity. This is accompanied by mucosal atrophy, which not only increases the risk for gastric and duodenal ulcerations but also reduces the intestinal surface for drug absorption [6]. To what extent drug absorption is affected solely by age-related alterations in the gastrointestinal tract remains to be elucidated.

Reduced liver mass, liver perfusion, and related metabolic changes have been reported [7, 8], but also raised the question of clinical relevance. Interestingly, reduced levels of cytochrome P450 have been found for CYP2E1, CYP3A, and NADPH cytochrome c reductase, while others have not (see [8]). However, age-related alterations in liver parameters seem to have less impact on drug metabolisation than individual polymorphisms of liver enzymes or drug-drug interactions on the level of hepatic metabolisation [9].

As ageing is associated with a \sim 1-% reduction in skeletal muscle mass per year, in old people serum creatinine is not predictive for glomerular filtration rates or renal function. Therefore, algorithms have been established to estimate the glomerular filtration rate from serum creatinine. The Cockroft-Gault formula has been used extensively but seems to

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underestimate the glomerular filtration rate [10, 11]. Alternative approaches have been evaluated and found serum concentrations of urea to be a sensitive indicator of renal function in the elderly. Thus, using serum urea levels the Levey algorithm provides an accurate estimation of renal clearance [11]. Nevertheless, the Cockroft-Gault formula has been recently confirmed to be accurate and safe to adopt pharmacotherapy to reduced renal function (CrCl < 50 ml/min) in lung cancer patients [12].

A considerable dose reduction has to be taken into account as soon as the creatinine clearance (CrCl) of patients is < 50 ml/min independent of age [13]. Secondly, drugs with an extrarenal elimination < 50 % require a considerable dose reduction. Which drugs are mostly affected and how is the extent of dose reduction calculated? The database provided by the Clinical Pharmacology and Pharmacoepidemiology Department of the Medical University Heidelberg is very helpful and summarizes the pharmacokinetics of the most commonly used drugs including chemotherapeutics (<u>http://www.dosing.de</u>). Using these instructions, dose adjustment can easily be calculated if necessary. Alternative databases exist and drugs with corresponding pharmacokinetic parameters have been listed in a recent review [13].

In contrast to the decline in total body water, skeletal muscle mass, and renal function, ageing is accompanied by an increase in body fat. Consequently, hydrophilic drugs have a smaller apparent volume of distribution and lipophilic drugs have an increased volume of distribution with a potentially prolonged half-life [13].

Finally, bone marrow mass is reduced in elderly individuals and shows a reduced ability for regeneration. There seems to be a reduction of hematopoietic stem cells which accounts for delayed response rates to treatments with filgrastim, pegfilgrastim, or erythropoietin [14]. Consequently, elderly cancer patients have a higher incidence of myelosuppression and hematotoxicity [15].

Given these various changes in organ and tissue function, the interindividual variability in drug disposition is considerable in elderly persons. In 2008, Hurria and Lichtman summarized chemotherapeutic studies that included elderly patients with reduced performance and found in only 5 out of 18 studies an age-related decrease in drug clearance [15]. Thus, interindividual differences (genetic polymorphisms), comorbidity, and polypharmacy represent higher risk factors than age alone. In conclusion, the complexity of interactions between individual genetic background, comorbidity, polypharmacy, and age-related changes in pharmacokinetics justifies the general rule "start low, go slow".

Selected Chemotherapeutics in Elderly Patients

Alkylating Chemotherapeutics

This class of drugs includes cyclophosphamide, ifosfamide, melfalan, and temozolomide. Haematotoxicity is clearly the dose-limiting toxicity of these drugs. However, dose modification only due to age is not recommended and might preclude therapeutic success. Cyclophosphamide is metabolized by CYP3A and CYP2B families and adverse effects are expected from the toxic metabolite acrolein. However, a dose reduction by 20–30 % is only justified in case of impaired renal function, but not when it comes to the factor "age" [16]. Temozolomide has an excellent pharmacokinetic profile requiring no dose adjustment even under conditions of reduced renal function. Nevertheless, an age-related increase in the incidence of lymphopenia, neutropenia, and/or thrombocytopenia has been documented [17]. An association of the latter side effects with female gender has been observed as well.

Platinum Compounds

Platinum-containing chemotherapeutics, such as oxaliplatin, cisplatin, and carboplatin, are widely used and show severe side effects [18]. However, there is no evidence for dose adjustment based on age alone. Myelosuppression and peripheral neuropathy are commonly observed, severe side effects and in particular age-related hearing loss upon cisplatin administration have been reported [18].

Nephrotoxicity of cisplatin may lead to a salt-wasting syndrome which upon adequate treatment and hydration exerts an excellent prognosis with rapid recovery [19]. Thus, nephrotoxicity is not related to age, either [20]. Conversely, preexisting renal impairment requires dose adjustment or excludes cisplatin administration in particular in elderly [21].

Antimetabolites

The antimetabolite, 5-fluorouracil (5-FU), is commonly used in chemotherapeutic schemes [22, 23]. The pharmacokinetics of 5-FU are not altered in aged patients; however, an age-dependent increase in toxicity is observed with female preference. The latter is explained by a reduced dihydropyrimidine dehydrogenase activity, the crucial enzyme in 5-FU clearance [24]. Main toxicities involve diarrhoea, mucositis, and haematologic complications. In a retrospective comparison of efficacy and tolerability of 5-FU-based chemotherapies in colon cancer patients, older individuals performed similar and equivalent to younger patients [25]. Overall survival and response rates were not different between age groups. Thus, the authors conclude that palliative chemotherapy in colon cancer patients should not be withheld from elderly patients.

Capecitabine is a pro-drug of 5-FU with prolonged bioavailability and an improved spectrum of side effects. Due to metabolic activation, intact liver function is a prerequisite for the efficacy of capecitabine. Age does not affect the pharmacokinetics of capecitabine in the presence of intact renal function [23]. In patients with reduced CrCl (< 50 ml/min) dose adjustments are mandatory, while an administration < 30 ml/min is not recommended [26]. The spectrum of side effects (diarrhoea, nausea, vomiting, and stomatitis) is similar to 5-FU, but observed less often with capecitabine. The hand-foot syndrome has a higher incidence with capecitabine. Conversely, the incidence of myelosuppression is seen less often with capecitabine [27].

Anthracyclines

Anthracyclines have been widely established chemotherapeutics for a long time. With increasing age, they exert a progres-

Camptothecins

The pharmacokinetics of the topoisomerase I inhibitor, topotecan, depend on the CrCl and age of the patient. Thus, dose adjustment is required to reduce the risk of myelosuppression in particular in elderly individuals with reduced renal function [15].

The prodrug irinotecan is extensively metabolized by cytochrome P450-3A4 (CYP3A4), which is of clinical relevance. Improved toxicity profile and reduced incidence of severe neutropenia were observed following individualized dosing of irinotecan on the basis of a midazolam clearance test, which is indicative for CYP3A4 activity [29]. Commonly observed side effects include diarrhoea, nausea, vomiting, and asthenia. Interestingly, genetic polymorphisms in the mannose-binding lectin are associated with a higher risk for irinotecan-induced febrile neutropenia corroborating individual stratification of chemotherapy [30].

Discussion

Age Per Se Is Not a Limiting Factor for Chemotherapy

There is accumulating evidence from retrospective studies and subset analyses that older cancer patients benefit from optimum chemotherapy comparable to younger individuals [31]. However, there is a lack of information from prospective studies. Thus, the occurrence of increased toxicity rates in older patients with multiple comorbidities and therefore the risk of drug-drug interactions have lead to a reluctance to treat older patients with biologicals [31]. Consequently, the inclusion of older patients into such clinical trials is urgently needed and adapted study designs have been suggested [32]. Additionally, usage of a geriatric assessment scoring system may facilitate identification of those patients who most likely benefit from optimum treatment (see [33]).

The parameters for decision of therapy have been recently evaluated in elderly patients with incurable non-small cell lung cancer [34, 35]. The driven force for conventional chemotherapy was the aggressive tumour species, while reluctance to receive chemotherapy led to gefitinib administration. Interestingly, the patient's age had no influence on therapeutic decisions.

General Considerations of Chemotherapy in the Elderly

Aged patients suffer from decreased symptom awareness. Therefore, physical activity is relevant in elderly patients and may improve their overall performance. Preliminary evidence from lung cancer patients before and after surgery corroborates that exercise therapy is safe and feasible. Thus, physical activity may be an important consideration in the multidisciplinary management of oncologic patients [36]. Moreover, diagnosis and treatment of complications are delayed, eg, skin alterations, febrile neutropenia, or thrombopenia-related bleedings [37, 38]. Consequently, there is already an attitude to manage side effects by proper observation and thereby to enhance the tolerability of chemotherapy in the elderly [39].

Comorbidity

In general, comorbidities in elderly cancer patients have a bad prognosis, which upon chemotherapy lead to inferior survival and outcomes. These patients are generally not included in clinical trials [35, 40]. Thus, limited information is available on comorbidities. In addition, comorbidity and polypharmacy are highly prevalent in the elderly.

Besides the aforementioned interactions in various organ systems, cardiovascular interactions, in particular ischemic complications, are often seen in high-dose chemotherapy [28, 41]. The spectrum of cardiac side effects of cancer chemotherapy has expanded with the development of combination, adjuvant, and targeted chemotherapies [41]. The cardiac toxicity of anthracyclines has been well-described for a long time and prevented by a dose limitation [28]. Similarly, high doses of cyclophosphamide or ifosfamide also have the potential to develop reversible heart failure and arrhythmias. More often, antibody-based targeted therapies and tyrosine kinase inhibitors are associated with heart failure, hypotension, or hypertension [41]. The molecular mechanisms are so far not clear in the latter cases. Thus, patients with pre-existing cardiovascular risks may substantially improve from referral to a cardiologist for close monitoring of their cardiovascular parameters.

Genetic Background and Polymorphisms

Targeted therapy does not only involve new therapeutics but also exact diagnosis of the individual tumour species and identification of genetic polymorphisms affecting drug pharmacokinetics [42, 43].

Very recently, genetic polymorphisms have been described in the ATP-binding cassette gene B1 (ABCB1, P-glycoprotein) of patients diagnosed with advanced gastric cancer and treated with second-line chemotherapy [44]. The AGCB1 transporter is in part responsible for resistance to several anticancer agents due to extrusion from tumour cells. This mechanism also alters the pharmacokinetics of these drugs with possible impact on therapeutic success. Interestingly, the 3435 CC polymorphism of ABCB1 was significantly associated with longer progression-free survival compared to the CT/TT type polymorphism. The cost-efficient availability of high-throughput techniques may allow for such an individualized genomic approach to identify biomarkers or susceptibility to new pharmacotherapies [42]. Moreover, pharmacogenetic studies are needed to identify genetic polymorphisms in distinct ethnic groups and gender to further optimize pharmacotherapies (see [43]). Finally, these findings will definitely improve individualized drug response and prevent inefficacies and toxicities of anticancer drugs particularly in the elderly.

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Conflict of Interest

The author states that no conflict of interest exists.

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