Chemotherapy dosing in elderly cancer patients – SIOG guidelines

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Cancer is mainly a disease of the elderly but clinical studies have generally excluded the elderly population for various reasons. Chemotherapy is one of the strongest weapons against (metastatic) cancer, but its use in the elderly has been limited due to fear of inducing toxicity. Ten important 'commandments' that need to be taken into account when prescribing chemotherapy to elderly patients will be discussed: treatment individualisation, comprehensive geriatric assessment, supportive therapy, drug interactions, compliance, alternatives to cytotoxic chemotherapy, hydration status, aim of chemotherapy, specific pharmacological data for specific chemotherapeutics. Concerning the last item, the International Society of Geriatric Oncology (SIOG) has reviewed the available information with regard to chemotherapy and aging. Extrapolation of data from younger to older patients is necessary, particularly to those patients older than 80 years, for which data is almost entirely lacking. A brief overview on drug dosing related to age will be presented concerning the most important classes of chemotherapeutic drugs, including alkylators, antimetabolites, anthracyclines, taxanes, camptothecins and epipodophyllotoxins.

Ten 'commandments' when giving chemotherapy to elderly patients:

(1) *Treatment individualisation*: Although alterations to some physiological functions with age have predictable PK or PD consequences, there is tremendous heterogeneity within the elderly population. Cancer chemotherapy in the elderly can best be considered as an example of the need for dose optimisation in individual patients.

(2) *Perform a complete geriatric assessment*: A comprehensive geriatric assessment (CGA), evaluating functional status, comorbidity, socioeconomic condition, nutrition, polypharmacy, and the presence or absence of geriatric syndromes, is indispensable in the treatment of elderly cancer patients [1], and has been shown to improve therapeutic outcome [2].

(3) *Supportive or protective agents can be very useful*: Supportive or protective agents such as haematological growth factors can play a key role in diminishing toxicity in the elderly. International guidelines on the use of prophylactic colony stimulating factors (CSF) [3] emphasise that patients aged 65 or older are at higher risk of febrile neutropenia and should therefore be evaluated for the prophylactic use of CSF, certainly for patients with diffuse aggressive lymphoma treated with curative chemotherapy. Haemoglobin levels should be maintained at 12 mg/dl or higher, for instance with erythropoietin, since anaemia may enhance the risk of chemotherapy related toxicity and is also associated with anaemia related symptoms that can decrease quality of life.

(4) *Beware of the risk of drug interactions*: Since many elderly patients are on multiple medications, there can be a great influence on the pharmacokinetics of anticancer drugs [4].

(5) *Compliance needs to be monitored*: This is not an issue for most anticancer treatments, which are given intravenously in hospital. However, in the case of domiciliary treatments such as oral cytotoxics, oral antiemetics, or subcutaneous growth factors, close supervision is necessary.

(6) *The possibility of less toxic therapy*: Older cancer patients (>70 years) undergoing classical chemotherapy are at higher risk of experiencing toxicity. Several studies show that chemotherapy is generally well tolerated with a limited impact on independence, comorbidity, and quality of life, but a selection bias might be present. Hormonal therapy or new molecular approaches such as signal transduction inhibition are promising in the elderly, because of the frequent lack of side effects associated with classical cytotoxic drugs.

(7) *Maintain adequate hydration*: Elderly patients have a tendency to drink less, especially when feeling ill, and are more intolerant of dehydration. Poor hydration can lead to decreased clearance and increased toxicity, especially for drugs subject to renal excretion.

(8) *Define the aim of chemotherapy*: It is very important to determine the goals of therapy before commencing treatment in elderly cancer patients. Firstly, it is vital to assess whether the patient can actually tolerate chemotherapy. In frail patients, or patients with considerable comorbidity, supportive care only is often the best course of action, even when tumours are potentially curable. In the curative or adjuvant setting, it is important to try to maintain dose intensity, because in both situations there is a steep dose response curve, and a small decrease in dose intensity can lead to a significant decrease in response and cure rates. Dose reductions or delays, which occur more frequently in elderly patients, can jeopardise survival benefit, especially in the adjuvant setting. For the palliative situation of incurable metastatic disease, the situation is different; whilst the effect of dose intensity on response rates has been demonstrated, it should be remembered that the aim is palliation, and that the survival advantage is often small. In this group, more efforts should be made to avoid toxicity, which can be aided by pharmacological considerations.

(9) *Check renal function in elderly cancer patients*: Prior to drug therapy in elderly patients with cancer, assessment and optimisation of hydration status and evaluation of renal function to establish any need for dose adjustment is required. Serum creatinine alone is insufficient as a means of evaluating renal function. More accurate tools, including creatinine clearance methods such as The Cockcroft–Gault method (CG) are available and are generally good indices of renal function status of the patient. However, in elderly patients, the CG and other similar formulas are not as accurate as in the younger population. More recently developed tools, such as the aMDRD, may be the estimation of choice in elderly patients whereas the CG estimate can be used in subjects younger than 65 years. However, the aMDRD has generally not been validated for dose calculation of chemotherapy, and the CG may be more practical. Moreover, in extremes of obesity and cachexia and at very high and low creatinine values, no single tool is really accurate. The best estimate of GFR is provided by direct methods such as ^{51}Cr-EDTA or inulin measurement. Within each drug class, preference may be given to agents less likely to be influenced by renal clearance. Within each drug class, preference may be given to agents less likely to be toxic to the kidneys or for which appropriate methods of prevention for renal toxicity exist. Co-administration of known nephrotoxic drugs such as NSAID should be avoided or minimised. The international society of geriatric oncology (SIOG) has elaborated guidelines on dose adaptation of chemotherapy in renal dysfunction [5].

(10) *Be aware of clinical data for specific chemotherapy drugs*: The SIOG guidelines [6] and other reviews [7] elucidate factors that can influence the pharmacokinetics of specific anticancer drugs frequently used in the elderly, and the clinical or biochemical parameters that could form the basis for dose adjustments with age. However, it should be stated that dose adaptation based on age related pharmacological changes is an unvalidated approach since clinical trials prospectively testing the efficacy and toxicity of age related dose adaptation versus standard dosing are lacking. A summary of frequently used chemotherapeutics is given in Table 1.

Conflict of interest statement

None declared.

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Table 1
Age related effects on pharmacokinetics of frequently used chemotherapeutics and consequences (based on refs. [6,7])

Chemotherapeutic	Effects and consequences
Alkylating agents	
Cyclophosphamide	– PK not different, some increased toxicity on PD level – Important liver metabolisation, effect of age related decrease in hepatic function is unknown – Adapt to renal function – No arguments for *a priori* dose reduction in elderly
Cisplatin	– Increased AUC and toxicity in elderly – Adapt to renal function – Consider the lower range of dosage (e.g. 60 mg/m^2) and preferably at a reduced infusion rate (e.g. over 24 h)
Carboplatin	– Adapt to renal function (Calvert formula)
Taxanes	
Paclitaxel	– Conflicting PK data on paclitaxel clearance in elderly – Several trials show feasibility of both every three weeks and weekly paclitaxel in elderly patients – No arguments for *a priori* dose reduction in elderly
Docetaxel	– Docetaxel PK is at most only minimally influenced by age – elderly patients are somewhat more vulnerable to side effects, but like for PK, interpatient variability is larger than age related variability – In principal, standard regimens of docetaxel can be used (dose and schedule depend on clinical setting) but high dose needs to be given with caution.
Topoisomerase inhibitors	
Etoposide (topo II)	– High variability in oral absorption – Increased AUC and toxicity in elderly – Dose adaptation according to albumin, bilirubin, renal function should be considered
Irinotecan (topo I)	– Increased AUC and diarrhoea in elderly – A lower dose (e.g. 300 mg/m^2 q3w instead of 350 mg/m^2 q3w) should be considered for age $\geqslant$70
Topotecan (topo I)	– Adapt to renal function – Consider weekly regimens (less myelosuppression)
Antimetabolites	
Methotrexate	– AUC possibly increased – Adapt to renal function
Fluorouracil	– PK and toxicity not majorly influenced
Capecitabine	– Lower dose such as 1000 mg/m^2 bid instead of 1250 mg/m^2 seems equally effective with less side effects – Adapt to renal function
Gemcitabine	– Unpredictable PK – Generally good tolerance in elderly
Fludarabine	– PK and toxicity not majorly influenced – Adapt to renal function
Antitumour antibiotics	
Doxorubicin	– Increased peak plasma concentrations – Increased myelosuppression and cardiotoxicity – At full dose (CHOP, AC) relatively toxic – Possible solutions: • Dose reduction • Alternative administration regimens: e.g. weekly • Liposomal forms • (Removal of doxorubicin in lymphoma regimens) • Growth factors

PK = pharmacokinetics; AUC = area under the curve; PD = pharmacodynamics.