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Mastering chemotherapy dose reduction in elderly cancer patients

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ABSTRACT

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. This review points out 10 recommendations that need to be taken into account when prescribing chemotherapy to elderly patients: aim of chemotherapy, specific pharmacological data for specific chemotherapeutics, treatment individualisation, alternatives to cytotoxic chemotherapy, comprehensive geriatric assessment, supportive therapy, hydration status, drug interactions, and compliance. Each of these topics will be reviewed here trying to give concrete recommendations for clinical practice.

1. Introduction

Chemotherapy is one of the strongest weapons in the fight against cancer. The fear of side effects by physicians has limited its use in elderly patients, but several trials have clearly shown that chemotherapy is feasible in elderly cancer patients. The high variability of patients' individual health status constitutes a major challenge in offering chemotherapy to older cancer patients, especially in the palliative setting. Oncologists feel fairly confident in predicting the risk of toxicity of a young patient, but they often feel much less certain about the ability of their older patients to tolerate treatment. They therefore feel trapped between two dangers: inducing severe toxicity, or giving inadequate treatment because of excessive fear of toxicity. Modifications to vital functions and altered physiology are known to occur with age. These changes can have a considerable impact on the pharmacokinetic (PK) processes of absorption, distribution, metabolism and excretion and the pharmacodynamic (PD) properties of administered drugs.[1] For many drugs with a high therapeutic index, this will be clinically unimportant, but for anticancer drugs, which usually have a low therapeutic index, these pharmacological changes can lead to dramatic consequences, such as excessive drug levels and unacceptable toxicity, or subtherapeutic drug levels and ineffective treatment. This review focuses on 10 recommendations that need to be taken into account when the indication and dose of chemotherapy is considered in elderly patients (Table 1).

2. Recommendations

2.1. *Define the aim of chemotherapy (Table 2)*

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

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Table 1 – Ten recommendations for the treatment of elderly cancer patients who are candidates for chemotherapy

Define the aim of chemotherapy
Be aware of clinical and pharmacological data for specific chemotherapeutics that suggest the need for dose modification in elderly
Treatment individualisation
The possibility of less toxic therapy
Perform a complete geriatric assessment
Supportive or protective agents can be very useful
Check renal function in elderly cancer patients
Maintain adequate hydration
Beware of the risk of drug interactions
Compliance needs to be monitored

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.[2] 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.[3,4] 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,[5] 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.

2.2. *Be aware of clinical data for specific chemotherapy drugs (Tables 3 and 4)*

An extensive review[1] elucidates 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. International Society Of Geriatric Oncology (SIOG) is also currently developing guidelines on this topic.

2.3. *Treatment individualisation*

Although alterations to some physiological functions with age have predictable PK or PD consequences, there is tremendous heterogeneity within the elderly population. Older patients differ more from one another than in the case of young individuals, by virtue of the accumulated effects of multiple disease processes and comorbidities, and the increased

Table 2 – Purpose of treatment in elderly cancer patients and the consequences (with permission from Ref. 1)

	Curative setting	Adjuvant setting	Palliative setting
Setting	Curative intent in advanced disease	Curative intent in (possibly) micrometastatic disease	Palliative intent in advanced disease
Examples	Germ cell tumours, lymphomas	Adjuvant setting in breast cancer, colon cancer, ovarian cancer	Advanced disease in cancer of the breast, colon, lung, prostate
Attitude	Some toxicity is acceptable, if it is well managed	Always weigh advantage (usually rather small) versus disadvantages (toxicity, morbidity of treatment)	Quality of life is paramount, significant toxicity is generally not acceptable
Dose intensity	Aim to maintain dose-intensity to optimise chances of cure, but remember pharmacological principles and alterations in the elderly	Dose intensity can be very important in order to have any gain at all, but remember pharmacological principles and alterations in the elderly	Definitely consider dose modifications based on pharmacological parameters and alterations in the elderly

Table 3 – Pharmacokinetic parameters that might change with aging (adapted from Ref. 2)

Parameter changes	Clinical consequences
Absorption: decreased	Oral chemotherapy (e.g. capecitabine) might be less effective in the elderly
Volume of distribution: decreased	Serum concentrations and toxicity of several chemotherapeutics might increase (e.g. cisplatin, taxanes, etoposide, irinotecan)
Hepatic metabolism: decreased	Not well known, may affect serum concentrations of chemotherapeutics elimitated by hepatic metabolisation (e.g. taxanes, cyclophosphamide, anthracyclines)
Renal excretion: decreased	Dosing should be adapted to present recommendations (ref) in order to avoid excessive serum concentrations and toxicity from renally excreted chemotherapeutics (e.g. carboplatin, topotecan, methotrexate)

Table 4 – Age related effects on pharmacokinetics of frequently used chemotherapeutics and consequences (based on Ref. 1)

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
- Ifosfamide
  - Increased area under the curve (AUC) in elderly
  - Adapt according to renal function and albumine level
  - Consider protracted infusion regimens and dose adaptation
- Melphalan and dacarbazine
  - Adapt to renal function
  - No arguments for a priori dose reduction in elderly
- Temozolomide
  - PK not different, but increased myelosuppression
  - No arguments for a priori dose adaptation
- 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)

Vinca alkaloids

- Vinorelbine
  - Conflicting PK data
  - Generally good tolerance, so no arguments for a priori dose reduction in elderly

Taxanes

- Paclitaxel
  - Conflicting PK data on paclitaxel clearance in elderly
  - Several trials show feasibility of both every 3 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 $\geqslant$ age 70
- Topotecan (topo I)
  - Adapt to renal function
  - Consider weekly regimens (less myelosuppression)

Antimetabolites

- Methotrexate
  - AUC possibly increased
  - Adapt to renal function

Table 4 – *continued*

- 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
- Idarubicin
  - Probably increased AUC
  - Adapt to renal function
  - No good data on drug dosing in elderly
- Mitoxantrone
  - No PK differences, maybe increased myelosuppression
  - No arguments for a priori dose reduction in elderly
- Bleomycin
  - No data on systematic dose reduction in elderly
  - Adapt to renal function

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

potential for drug–drug interactions. Thus, cancer chemotherapy in the elderly can best be considered as an example of the need for dose optimisation in individual patients. In general, and for most drugs, age itself is not a contraindication to full dose chemotherapy. The main limiting factors are comorbidity and poor functional status, which may be present in a significant number of the elderly population.[6]

2.4. *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,[7] 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. Examples of effective and generally well tolerated new targeted therapies that might be used as monotherapy or in combination with 'soft' chemotherapy include trastuzumab in Her2 positive breast cancer, cetuximab concomitant with radiotherapy in head and neck cancer, bevacizumab in colorectal cancer, imatinib in chronic myeloid leukaemia.

2.5. *Perform a complete geriatric assessment (Table 5)*

A comprehensive geriatric assessment (CGA), evaluating functional status, comorbidity, socio-economic conditions, nutrition, polypharmacy, and the presence or absence of geriatric syndromes, is indispensable in the treatment of elderly cancer patients,[8] and has been shown to improve therapeutic outcome.[9]

2.6. *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

Table 5 – Recommendations on CGA (adapted from Ref. 8)

1. Biological and clinical markers for 'degrees of aging'. There are several specific elements that appear useful to integrate in the CGA of cancer patients
   - Biochemical markers such as albumin, haemoglobin, and creatinine clearance can provide prognostic information and clues as to tolerance to treatment
   - As for clinical markers, functional status assessment should be more extensive than the Eastern Cooperative Oncology Group (ECOG) performance status evaluation and may include activities of daily living (ADL)/instrumental activities of daily living (IADL), and/or a performance test such as the timed get up and go
2. CGA detects problems that cannot be detected by an oncologic assessment
   - CGA-based approach is strongly recommended in elderly patients to improve the detection of problems. Significant clinical information may be missed if a CGA-based approach is not pursued in the older cancer patients
   - The best form of geriatric assessment pertaining to cancer patients remains to be defined. In addition to the biological and functional assessment elements mentioned under Point 1, screening for depression and cognitive impairment should be conducted. As a practical example, a combination of tools frequently used in geriatric oncology comprises ADL/IADL, the Geriatric Depression Scale, and Folstein's Mini-Mental Status
3. CGA is effective
   - Although the best form of CGA for cancer patients remains to be defined, some form of geriatric assessment and intervention can be expected to improve independence, quality of life, and rate of hospitalisation of cancer patients, and be cost-effective
   - Any type of CGA intervention should include a follow-up, since this appears to be the key for effectiveness of CGA
4. Screening tools and their validity compared to full CGA?
   - 70 years of age seems an appropriate age level to start screening since the incidence of geriatric problems increases sharply after 70. This should be considered a soft limit
   - No single screening tool has been specifically tested in the older cancer patient, so any tool studied in the non-oncology setting can be used at present (such as the Groningen Frailty Index[16]). If the screening is positive, it should be followed by a more complete geriatric evaluation

CGA, comprehensive geriatric assessment; ECOG, Eastern Cooperative Oncology Group; ADL, activities of daily living; IADL, instrumental activities of daily living.

colony stimulating factors (CSF)[10,11] emphasise that patients aged 65 or older are at a 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[12] and is also associated with anaemia related symptoms that can decrease the quality of life.

2.7. *Check renal function in elderly cancer patients (Table 6)*

Prior to drug therapy in elderly patients with cancer, assessment and optimisation of hydration status and evaluation of the 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 (C–G) are available and are generally good indices of renal function status of the patient. However, in elderly patients, the C–G and other similar formulas are not as accurate as in the younger population. More recently developed tools, such as the abbreviated modification of diet in renal disease (aMDRD), may be the estimation of choice in elderly patients whereas the C–G 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 C–G 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

Table 6 – Frequently used formulas for the calculation of CrCl from SCr[a] (adapted from Ref. 13)

Method	Formula for renal clearance
Cockcroft–Gault	Estimated CrCl (mL/min) = [(140 − age) × weight]/[72 × SCr (mg/dL)] (×0.85 if female)
aMDRD[b]	Estimated CrCl (mL/min/1.73 m^2) = [186 × (SCr (mg/dL)$^{-1.154}$ × age (years)]$^{-0.203}$ × [0.742 if female] × [1.21 if African American]) to give result in mL/min × BSA/1.73

CrCl, creatinine clearance; SCr, serum creatinine; BSA, body surface area measured in square meters; aMDRD, abbreviated modification of diet in renal disease; BUN, blood urea nitrogen.

a SCr μmol/L = SCr mg/dL × 88.4.

b SCr measured by Jaffé method. If more standardised SCr measurements are used such as PAP, which have recently replaced Jaffé in many institutions, then SCr should be divided by a factor of 0.95.

growth factor receptor (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 proposed guidelines on dose adaptation of chemotherapy in renal dysfunction.[13]

2.8. *Maintain adequate hydration*

Elderly patients have a tendency to drink less, especially when feeling ill, and are more intolerant of dehydration. Adequate oral fluids should be specifically advised for older cancer patients during treatment with anticancer drugs. Poor hydration can lead to decreased clearance and increased toxicity, especially for drugs subject to renal excretion.

2.9. *Beware of the risk of drug interactions*

Since many elderly patients are on multiple medications, with 29% taking more than seven drugs, there can be a great influence on the pharmacokinetics of anticancer drugs. For instance, increased toxicity has been observed in patients receiving intermediate dose methotrexate and non-steroidal analgesics due to the decreased renal clearance of methotrexate. Major drug interactions can occur during hepatic metabolism, significantly influencing treatment efficacy and toxicity. This important subject is discussed elsewhere.[14,15]

2.10. *Compliance needs to be monitored*

This is not an issue for most anticancer treatments, which are given intravenously in the hospital. However, in the case of domiciliary treatments such as oral cytotoxics, oral antiemetics, or subcutaneous growth factors, close supervision is necessary.

3. Conclusion

The management of the elderly patient with cancer presents an increasingly common challenge. The elderly will often be the largest group of patients treated by the medical oncologist. Like pediatric oncology, also for geriatric oncology there are specific aspects related to age that require attention by the treating physician. The geriatric population is a priori heterogeneous population at all levels, and therefore it is very difficult to provide simple guidelines. A comprehensive geriatric assessment allows to detect other health problems that might interfere with the cancer treatment and outcome. Physicians should consider the use of supportive therapy and alternatives to cytotoxic chemotherapy, and should also check for drug interactions, compliance, and hydration status. When prescribing chemotherapy, the aim of chemotherapy should be specified since it can have impact on the choice of dosing. Lastly, oncologists should be familiar with the age related changes in physiology that affect the disposition and response to drugs in older patients. In general, and for most drugs, age itself is not a contraindication to full dose chemotherapy. By considering the basic principles of the PK and PD of these agents, therapy can be optimised. Renal function can be an important parameter for renally excreted cytotoxic drugs, since the renal function significantly declines with increasing age. For most agents, it is not possible to provide clear guidelines for dose modification on the basis of age. The decision to modify the dose of an anticancer agent is the responsibility of the clinician who must integrate knowledge of their pharmacology with the type of cancer and condition of the elderly patient. Further prospective studies on drug dosing are warranted in the elderly cancer population.

Conflict of interest statement

None declared.

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