Pharmacology

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Fitness for chemotherapy

Recent studies have documented that elderly people, who are carefully screened for any possible disease that could potentially modify bodily functions, have less function loss than reported traditionally [1,2]. However, an apparent excellent general condition can mask a significant loss of organ function. It is also documented that disease or stress can alter dramatically the delicate balance between existing functional reserves and normal physiological functioning [3]. Of particular importance for the discussion of the appropriate use of drugs in cancer therapy are changes in renal and hepatic function, as well as modifications of lean body mass and bone marrow reserves.

Renal function

One should always calculate the actual creatinine clearance in a particular patient using for example the formula of Cockcoft and Gault [4] which has been shown to be more reliable in elderly people than an evaluation based on standard 24 hour urine collections.

Liver function

Hepatic function can be modified in several ways by ageing: decreased blood flow, decreased albumin production and decreased cytochrome P450 function [5]. Decreased liver blood flow will result in decreased liver clearance for those drugs which are intensively extracted by the liver. Drugs with a lower extraction ratio are more affected by variations in protein-binding, and their liver metabolism increases dramatically with minor changes in the protein bound drug fraction. The balance of these two elements in elderly people is stated to result in a relative steady-state and may not have major implications for the use of cytotoxic agents. Much more important are changes in liver metabolic function, which need to be distinguished between phase I and phase II reactions. Phase I reactions involve drug metabolisation through hydroxylation, dealkylation and reduction and involve mainly the cytochrome P450 isoenzymes. Phase II reactions include conjugation (glucuronidation, sulphation), acetylation and methylation. Phase I reactions are possibly modified with advanced age, although this is controversial, while phase II reactions are not. However, concomitant use of several drugs by elderly people may lead to possibly clinically significant changes in cytochrome P450 function. A typical example of such changes is the induction of cytochrome P450 by phenobarbital and sex steroids, and its inhibition by cimetidine. Phase I reaction modifications can unpredictably affect cytotoxic agents like the oxazaphosphorines (cyclophosphamide, ifosfamide) which are activated and also deactivated by this mechanism.

Bone marrow reserves

Many cytotoxic agents are myelotoxic and unpredictable myelotoxicity can arise in elderly people, even if doses are adjusted to take into account differences in pharmacokinetics. Such observations are, however, mostly limited to frail (malnourished) patients.

Neurotoxicity

It is important to consider that many cytotoxic agents (vinca alkaloids, epipodophyllotoxins, taxoids and platinum derivatives) are neurotoxic, and to realise that an elderly person may be considerably handicapped by the loss of peripheral sensitivity. Even more dramatic can be ototoxicity which may lead to clinically significant hearing loss because elderly people have a limited acoustic reserve.

Principles of drug dosing

There is a correlation between functional status and toxicity of any cancer therapy, and the oncologist

will have to weigh several additional factors before deciding to use a determined chemotherapy. Once this choice is made, the doses and schedule of the chemotherapy may need some adaptation to changes in physiological parameters. These have been extensively reviewed and are summarised here [6].

Liver function abnormalities

If such abnormalities lead to an increased bilirubin level, several drugs have to have a dose adjustment. This is clearly not different in elderly or younger patients, although in both situations one has to rely on limited amounts of published data. Antimetabolites, epipodophyllotoxins (if renal function is normal), and most alkylating agents do not seem to be more toxic in these cases. Doses of anthracyclines and anthraquinones, except idarubicin, have to be reduced by 50% if bilirubin is above 26 μmol/l and by 75% if bilirubin is above 52 μmol/l. Idarubicinol is the active metabolite of idarubicin and the reason why the dose of idarubicin is not adapted in cases of increased bilirubin values as the metabolite is renally excreted. This means, however, that idarubicinol does need careful adaptation of the dose in cases of renal insufficiency, and such guidelines are not yet available. In cases of impaired hepatic function, vinblastine use needs to follow the same guidelines as suggested for the anthracyclines. Taxoids should be managed according to the same guidelines as anthracyclines. Docetaxel doses are reduced to 75% of the planned dose if there is a simultaneous abnormality of both alkaline phosphatase and transaminase values, even in the presence of normal bilirubin levels.

Renal function abnormalities

The Cockcoft and Gault formula is readily usable thanks to simple rulers, and has been shown to be a reliable method in patients up to the age of 75 years [4]. Oncologists are familiar with dose adaptations for carboplatin [7] and methotrexate [8]. The hepatic metabolism of taxoids, doxorubicin, epirubicin and vinca alkaloids in principle permits their use at full doses even if renal function is impaired. Epipodophyllotoxins can probably be used at full dose until a clearance of less than 0.42–0.50 ml/s occurs, if liver function is normal. The doses of bleomycin, carmustine, cisplatin, 2-CDA, camptothecin derivatives, cytarabine, fludarabine, ifosfamide and other agents need to be reduced as soon as the creatine clearance is below 1 ml/s, a commonly accepted limit. It is important to note that patients above 70 years of age are not different from younger patients when evaluated for cisplatin-induced nephrotoxicity and this has also been shown to be true for patients above the age of 80 years [9,10]. Thus, if thrombocytopenia is of concern, one can, in elderly patients who can tolerate a careful hyperhydration, use cisplatin instead of carboplatin.

References

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