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Perspectives and Commentaries

Chemotherapy in the Elderly

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(A COMMENT ON: Tirelli U, Carbone A, Zagonel V, Veronesi A, Canetta R. Non-Hodgkin's lymphomas in the elderly: prospective studies with specifically devised chemotherapy regimens in 66 patients. *Eur J Cancer Clin Oncol* 1987, **23**, 535–540.)

APPROXIMATELY 50% of all cancers are diagnosed in persons older than 65 years. This reality should be kept in mind when one goes through the oncological literature, which focuses generally on younger patients, and when one wants to apply the published treatments to routine practice.

Papers on diagnostic and therapeutic attitudes in elderly patients have recently started to appear in the literature. In a recent report, Samet *et al.* have reviewed the treatment used in 22,899 patients with malignant disease diagnosed between 1969 and 1982 and found that the proportion of cases receiving potentially curative therapy decreased with age [1]. Several potential factors may explain why treatment options in elderly patients differ from those used in younger patients: increased prevalence of associated chronic diseases, fear of increased toxicity of the treatment, absence of motivation and lack of social and familial support. All these considerations certainly apply to chemotherapy and, in particular, increased toxicity may be due to age-related changes in the pharmacokinetics and pharmacodynamics of the anticancer agents [2]. In addition, elderly patients, who often suffer from many chronic diseases, take several medications; this can lead to deleterious drug–drug interactions [2, 3].

One of the most important relationships in pharmacokinetics is that relating the dose, the area under the plasma concentration vs. time curve (AUC), which reflects the total exposure of the body to a drug, and the total body clearance of this drug: AUC = dose/total body clearance. From this equation, it appears that total body clearance is a main determinant for the AUC and therefore, for the biological effects of a drug.

In contrast, the elimination half-life is potentially misleading because it is related to two variables, the volume of distribution and the clearance: half-life = (0.693 × volume of distribution)/total body clearance. The volume of drug distribution may be modified by associated diseases (such as congestive heart failure or chronic renal disease), by changes in the percentage of adipose tissue and by alterations in the protein binding capacity. Since the half-life is under the influence of two parameters that can change concurrently in the same or in opposite directions, modifications of the half-life may be difficult to interpret [2].

Because of the importance of the total body clearance for the effect of a drug, it would be useful to be able to predict the clearance and adjust the dosage accordingly. For drugs excreted by glomerular filtration, the creatinine clearance can give an estimate of the drug total body clearance. Substantial decreases in glomerular filtration rate and renal blood flow occur with aging. Therefore, one can expect reduced clearance for drugs such as cisplatin, methotrexate or bleomycin and one should use these agents only after a determination of the creatinine clearance; this requires a reliable urine collection which may not be easy in the elderly. Serum creatinine alone, which reflects not only creatinine clearance but also creatinine production (which in turn reflects muscle mass and muscle turnover) may be a potentially misleading index of renal function. It is well known that a

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significant and clinically important reduction in creatinine clearance may occur with very little change in serum creatinine.

The liver is a much more complicated organ and there is no straightforward and generally available laboratory test that can predict drug metabolizing capacity in an individual patient. In addition, the liver has a very large metabolizing capacity: profound hepatic alterations may be necessary to alter drug clearance, but the threshold above which drug clearance is reduced is unknown. Thus, guidelines to adjust the dosage of the many drugs cleared by the liver are, at present, lacking.

How does clinical experience fit with these theoretical considerations? Data on the administration of *standard* doses of chemotherapy to elderly patients show that, overall, the older patients tolerated the treatment as well as younger patients [4, 5]. Response and survival rates are comparable in older and younger patients. However, in these studies, the prevalence of elderly patients was lower than the prevalence of elderly patients in the general population. Thus, these studies were to some extent biased by selection criteria, and one cannot conclude that *any* old patient can be treated safely with standard dosages of chemotherapeutic agents.

When *intensive* chemotherapy is being used, the situation may be quite different [6]. In a randomized trial, 40 patients with acute leukemia older than 70 years received either full dose or attenuated dose combination chemotherapy with daunorubicin, cytosine arabinoside and 6-thioguanine. The two regimens differ mainly by the dosage of daunorubicin, that was equal to 60 mg/m^2/day on days 1–3 in the full dose regimen and to 50 mg/m^2/day on day 1 in the attenuated regimen. The response rate was similar in the two arms. However, there were 12 early deaths in the full dosage arm vs. five early deaths in the attenuated arm ($P = 0.05$) and the median survival was shorter for the patients treated with the full dose regimen (29 days) than for the patients treated with the attenuated dose regimen (150 days) ($P < 0.02$).

The comparison of the results from these studies may suggest that, while the efficacy and the toxicity of the standard dose chemotherapy are comparable in older and younger patients, older patients tolerate intensive chemotherapy poorly. Reduction in drug clearance may be one of the reasons for poor tolerance of elderly patients to intensive chemotherapy; reduced clearance leads to increased AUC and increased biological effects, which, for intensive regimens, may fall in the lethal range.

The study by Tirelli *et al.*, recently reported in the *European Journal of Cancer and Clinical Oncology* [7], is important in view of the limited information available on the treatment of non-Hodgkin lymphomas in the elderly. Sixty-six patients older than 70 years were investigated; the majority had stage III or IV disease. Forty-five patients were previously untreated; 47 had tumors of intermediate or high grade according to the Working Formulation. The authors used two different regimens: teniposide (100 mg/m^2 i.v. weekly) or etoposide + prednimustine (100 mg/m^2 for 5 days every 3 weeks orally for the two drugs). As these dosages are in the standard dose range, one should expect these regimens to be well tolerated by the patients. Indeed, severe toxicity was observed in only 3.2% of the courses. There was only one leukopenia-related death.

The overall response rate was 53% with 38% complete responses. The overall and disease-free survival rates at 3 years were 21 and 12%, respectively. For the subgroup of 15 patients with diffuse histiocytic lymphomas, the complete response rate was 53% with overall and disease-free survival rates at 3 years of 47 and 27%, respectively.

In a disease as heterogeneous as non-Hodgkin's lymphomas, great caution should be exerted in the historical comparison of the antitumor efficacy and toxicity of different therapeutic regimens. Although the combination of cyclophosphamide–doxorubicin–vincristine and prednisone (CHOP) was associated with excessive toxicity in elderly patients in one study [8], the same combination was very active and well tolerated when given at initially reduced dosages followed by dose escalation according to the degree of myelosuppression [9]. In younger patients with malignant lymphomas, the best results are currently achieved wih the so-called third generation regimens [10]. As discussed earlier, it is unlikely that elderly patients could tolerate these intensive regimens. However, their use in this group of patients should perhaps be explored with appropriate initial dose reduction and subsequent escalations.

The development of new regimens, specifically designed for elderly patients, is an important and laudable goal. The regimens based on a podophyllotoxin derivative with or without prednimustine reported by Tirelli *et al.* fall into this category. Another important area of research is the adaptation of regimens of established efficacy to the tolerance of elderly patients. Arbitrary dose reductions and reescalations such as those used in the study with the CHOP regimen [9] constitute a very empiric way to reach this goal. It would be of great interest to be able to adapt the dose in each individual patient to his pretreatment clinical and laboratory characteristics. This will require detailed clinical and pharmacokinetic studies. Given the difficulties of clinical research in elderly patients [11], these studies may have to be per-

formed first in younger patients. Such an approach would represent an important achievement for elderly patients, but would also benefit to the younger patients.

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