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CORRESPONDENCE

Old Age: Biologic Versus Chronologic

TO THE EDITOR: We read with great interest the article by Goldberg et al[1] reporting the results of a "Pooled Analysis of Safety and Efficacy of Oxaliplatin Plus Fluorouracil/Leucovorin Administered Bimonthly in Elderly Patients With Colorectal Cancer" published in the September 1, 2006, issue of the *Journal of Clinical Oncology*.

The elderly population represents a heterogeneous group of patients frequently undertreated due to their age, although benefits of therapy could be overlapped with their younger counterpart.[2]

Optimal treatment of elderly patients affected by colorectal cancer is a fascinating challenge, and treatment providers have to consider not only the chronologic age of their patients, but also medical and physiological characteristics and mainly their biologic age. The introduction of new and active drugs into clinical practice, such as oxaliplatin, has stimulated clinical research.

Pharmacokinetic oxaliplatin has been well-delineated and is characterized by a rapid plasmatic disappearance and by metabolic biotransformations that are not cytP-450 mediated. Drug excretion occurs predominantly in the urine (equal to 53.8 ± 9.1% of the platinum dose) and unbound platinum clearance is significantly correlated with glomerular filtration rate and creatinine clearance.[3] No increase in toxicity has been reported in patients with mild and moderate renal impairment even though they are exposed to increased platinum circulating concentration, and no correlation has been found between platinum clearance and hepatic disfunction, age, and sex.[4]

These data confirm that we do not have to expect a different pattern of oxaliplatin-related toxicity in the elderly. How could we suppose a different pattern of toxicity based only on age?

The evidence regarding the tolerability and efficacy of anticancer treatments for elderly patients affected by colorectal cancer derives from two different sources: retrospective analyses conducted on the subgroup of elderly patients enrolled onto clinical trials that did not have an upper age limit and prospective clinical trials specifically designed for elderly.

Although the Goldberg et al[1] study enhances our knowledge on this matter, as they mentioned in their Conclusion, it is possible to argue that when clinical trials are designed to test the efficacy of a treatment intended for younger patients, only a selected proportion of elderly patients will be considered for enrollment, and so the results may not necessarily be extended to the general nonselected elderly population.[5]

Moreover in the studies selected by Goldberg et al, the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial[6] had the lower accrual rate of elderly patients, probably due to the adjuvant setting and to a previous selection based on a benefit/risk rate, performance status, and chronologic age—an indirect confirmation derived from the other selected trials, in which the higher elderly accrual rates were for patients with metastatic disease.

Age was not associated with differences in progression/disease-free survival ($P = .70$). In all patients, the combination of oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) was associated with improved progression/disease-free survival overall, and this did not differ by patient age ($P = .42$ for age-treatment interaction). Moreover the relationships among age, treatment, and overall survival did not change when age was modeled as a continuous variable, which lead us to believe that the elderly population probably overlap the younger one, receiving the influence of a single good prognosis group not particularly influenced by age (performance status 0 to 1, medical and physiological characteristics, absence of comorbidity).[7] This impression could be indirectly confirmed by the rates of any grade three or higher adverse events that did not differ by age group when age was modeled as either a dichotomous or continuous variable. Heterogeneity of population, adjuvant, first-line, and second-line patients, didn't help us to discriminate the influence of age on real toxicity and efficacy.

We believe that this pooled analysis adds new information about elderly patients and chemotherapy, but a new generation of specifically designed clinical trials for the elderly population are eagerly awaited and should include the development and validation of new measures and tools to better define biologic versus chronologic age.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

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