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Relation between age and clearance rate of nine investigational anticancer drugs from phase I pharmacokinetic data

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Abstract. Aging influences the disposition and effects of several classes of drugs. Although drug clearance rate is correlated with toxicity for many anticancer drugs, few data have been published concerning the relationship of aging and clearance of chemotherapy. This study was performed to identify any relationship between age and clearance rate for anticancer drugs in phase I trials at the Johns Hopkins Oncology Center. In a retrospective study, we examined the clinical and pharmacokinetic data for 344 adults (aged 21–77 years) who received 9 phase I drugs with linear clearance in 13 clinical trials. We sought correlations between age and clearance for each drug and for the whole group. Data available for 9 of the 13 trials were used to compare age (<65 or >65 years) versus dose delivered [$<$ the maximum tolerated dose (MTD) vs $\geq$ the MTD] or toxicity ($<$ grade 3 vs $\geq$ grade 3). Of 344 patients, 81 (23.5%) were >65 years old, 34 (9.9%) were ≥ 70 years old, and 5 (1.5%) were ≥ 75 years old. There was no significant correlation between drug clearance and age for individual drugs or the group as a whole. There was no significant difference between patients of the older and younger age groups with regard to dose or toxicity. Although only a small number of patients aged ≥ 75 years were treated, our results suggest that the elderly do not experience greater toxicity even when treated at doses comparable with those given younger patients and should not be excluded from phase I trials on the basis of age. As the population of the United States ages, more elderly patients will be candidates for chemotherapy. A more thorough examination of the relationships between age, clearance rate, and toxicity can be accomplished as active drugs enter phase II/III studies.

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Introduction

Aging influences the disposition and effects of several classes of drugs. Declines in renal and hepatic clearance and decreases in end-organ functional reserve have been identified in aging populations [2, 3, 5, 7, 9, 16, 22, 29]. Age-related declines in drug elimination have been shown to alter the disposition of antineoplastic drugs such as methotrexate (MTX) [5, 15]. In addition, some studies have implicated declines in the reserve capacity of target organs (e.g., bone marrow) in worsened toxicity [3, 17]. Although reduction in drug clearance is often felt to be the most important parameter that influences the toxicity of antineoplastic agents [8], the effect of the aging process on drug clearance has not been delineated for most antineoplastic agents.

A correlation between drug disposition and age might occur for new drugs with predominately renal clearance such as hexamethylene bisacetamide (HMBA) [25]. Clearance of drugs that are predominately eliminated by hepatic processes might also be altered in aging patients (e.g., paclitaxel and trimetrexate, TMTX [10, 18]). However, many of the drugs are known to have multiple pathways of clearance and some of the drugs' elimination pathways are undefined [1, 6, 10–14, 18, 20, 24–28].

This study was performed to identify relationships between age and clearance rates for investigational anticancer drugs evaluated in phase I trials at the Johns Hopkins Oncology Center. Any significant relation found would be important for identifying age as a variable that predicts altered drug disposition and for anticipating differences in drug efficacy and toxicity.

Materials and methods

Clinical and pharmacokinetic data from adults receiving 9 antineoplastic drugs in 13 phase I trials between 1982 and 1992 were reviewed. All studies using drugs with linear nonsaturable elimination processes were included. The drugs studied were an antimicrotubule agent, paclitaxel; three antimetabolites, trimetrexate, dichlorometho-

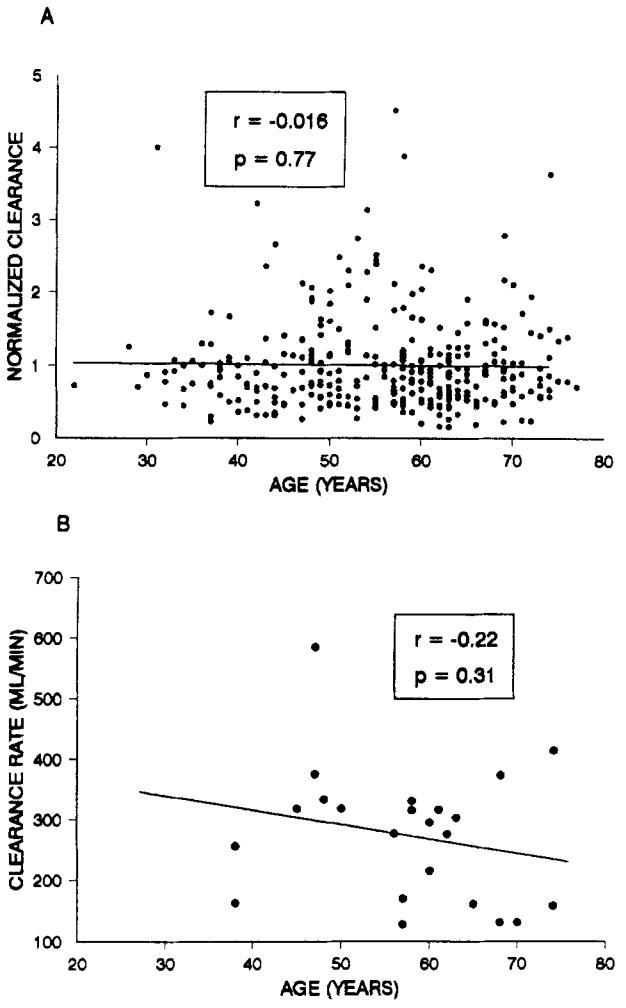

Fig. 1. **A** Drug clearances normalized as the ratio to the mean versus patient age (n = 344). **B** Clearance rate of DCMTX versus patient age

trexate, and brequinar; two DNA-intercalating agents, piroxantrone and menogaril; two differentiating compounds, *N*-methylformamide (NMF) and HMBA; and a topoisomerase I inhibitor, topotecan.

Patients studied in all trials except for the TMTX-organ dysfunction trial met the following requirements: (1) an age of >18 years, (2) adequate hepatic function (plasma bilirubin concentration, <2 mg/dl), (3) adequate renal function (plasma creatinine concentration <1.5 mg/dl), (4) an Eastern Cooperative Oncology Group (ECOG) performance status of 3 (capable of performing minimal self-care) or lower, and (5) the absence of concomitant illnesses that might increase risks of toxicity. For the trial evaluating TMTX in patients with reduced organ function, the above criteria were followed except that the plasma bilirubin level ranged from 0.2 to 15.3 mg/dl (mean, 2.1 mg/dl) and the serum creatinine concentration ranged from 0.7 to 2.6 mg/dl (mean, 1.25 mg/dl). Details of drug administration and pharmacokinetic analysis of drug disposition have been published previously [1, 6, 10–14, 18, 20, 24–28].

Relationships between individual drug clearance rates and age were evaluated using linear regression analysis (Stat Soft Inc., Tulsa, Okla.). Drug clearance rates were obtained from the data sets described above [1, 6, 10–14, 18, 20, 24–28]. Birth dates in the on-line data base at the Johns Hopkins Oncology Center were used to calculate age on the 1st day of treatment. For comparison of drug clearance rates for the entire group of drugs, drug clearances for each drug were normalized as a ratio to the mean clearance for that drug. To confirm that expected declines in renal function were seen in the population studied, the creatinine clearance rate was calculated using the pretreatment weight and serum creatinine value, adjusted for sex by the method of Cockcroft and Gault [4].

For individual correlations between age and drug clearances that had correlation coefficients (r) of greater than 0.3 or less than -0.3, the slope of the regression line and 95% confidence limits for the slope were calculated. The relationship was considered significant only if the 95% confidence limits did not include a slope of zero. This calculation and all correlations were made with CSS Statistica (Stat Soft Inc., Tulsa, Okla.).

Relationships between age and the delivered dose or toxicity were evaluated for 9 of the 13 trials for which data were available. Patients who received less than the defined maximum tolerated dose (MTD) were compared with those who were given doses equal to or greater than the MTD. Dose-limiting toxicity was measured by ECOG criteria [21] in trials conducted prior to 1990 and by Common Toxicity Criteria [19] in those carried out subsequently. Dose-limiting toxicities have been defined for each trial [6, 10–14, 20, 25, 28]. Hematologic toxicity was dose-limiting for six drugs: piroxantrone; brequinar; HMBA 10-day; TMTX, bolus; THTX, daily × 5; paclitaxel; and topotecan. The dose-limiting toxicity for dichloromethotrexate (DCMTX) was hepatic, whereas for NMF, oral, it was nausea, vomiting, malaise, and central nervous system disorders.

Data were analyzed using two-by-two tables of age (<65 or ≥65 years) versus dose (< MTD or ≥ MTD) or grade of dose-limiting toxicity (< grade 3 or ≥ grade 3). Fisher's exact test for comparison of proportions was used for individual drug trials and the chi-square test was used for the group as a whole (StatSoft Inc., Tulsa, Okla.).

Results

Of the 344 patients with pharmacokinetic data, 81 (23.5%) were ≥65 years old, 34 (9.9%) were ≥70 years old, and 5 (1.5%) were ≥75 years old. Table 1 lists the group characteristics and the correlation coefficients for age versus drug and creatinine clearance rates determined for 344 patients. The means and standard deviations for age and creatinine clearance were similar between the treatment groups. No correlation between age and the clearance rate of these drugs was identified. Of the 12 correlation coefficients calculated for drug clearance versus age, none of the values were statistically significant (range of r = –0.407 to 0.282, P = nonsignificant). Illustrated are the data for the entire group with clearance normalized to the mean (r = –0.016, P = 0.77; Fig. 1A) and DCMTX (r = –0.22, P = 0.31; Fig. 1B), an example of the scatter for an individual drug.

In the 9 trials for which toxicity data were analyzed (249 patients), 133 (53.4%) patients received ≥ the MTD, 76 (30.5%) developed ≥ grade 3 toxicity, and 54 (21.7%) were ≥65 years old. We found no relationship between age and delivered dose or toxicity in the 9 evaluable trials. In all, 28 (51.8%) of the patients aged 65 years and older and 105 (53.8%) of those aged <65 years were treated at a dose equal to or above the MTD. Overall, 14 (25.9%) patients aged ≥65 years and 61 (31.7%) patients aged <65 years had dose-limiting toxicity equal to or greater than grade 3. Fisher's exact test showed no significant difference between the older and younger age groups with regard to dose or toxicity for individual drugs or the group as a whole.

To demonstrate that these patients exhibited the expected decline in renal function with age, correlations between creatinine clearance rates and age were calculated for each drug studied and for the entire group of patients (Table 1). For the group of patients as a whole the corre-

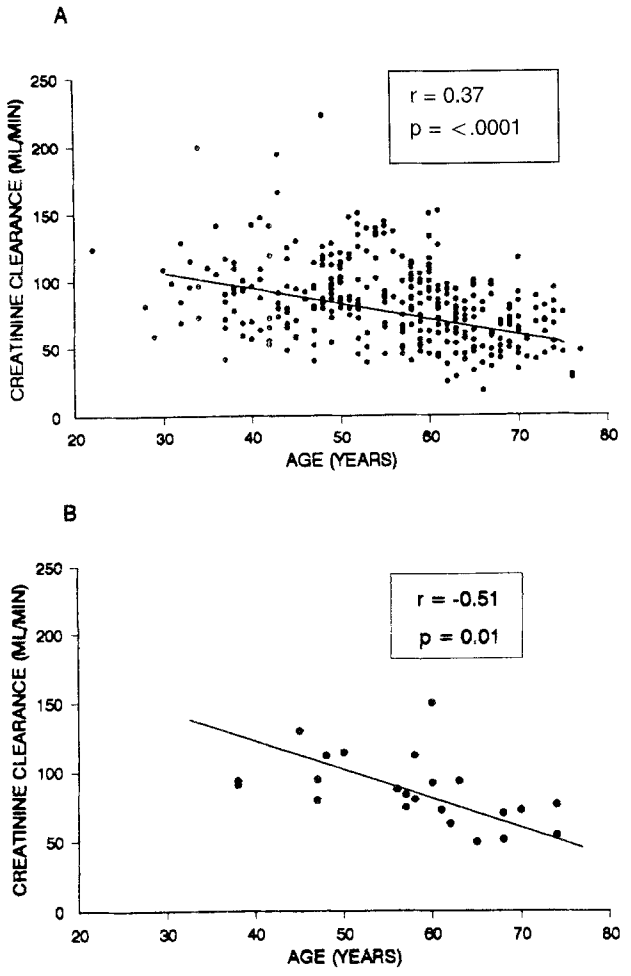

Fig. 2. **A** Creatinine clearance versus patient age (n = 344). **B** Creatinine clearance rate of DCMTX patients versus patient age

lation was, as expected, significant ($r = -0.37$, $P = < 0.0001$; Fig. 2A). Of 11 correlations between creatinine and age, 7 showed correlations similar to that illustrated by patients treated with DCMTX (r = –0.51, P = 0.013; Fig. 2B). Correlations between age and creatinine clearance rate were weaker for patients receiving NMF, intravenous; menogaril; HMBA, and paclitaxel. For one drug, HMBA, our sample sizes were inadequate for assessment of the relationship between age and drug or creatinine clearance rates.

Discussion

As our population ages, more elderly patients in generally good health will be candidates for chemotherapy. Although relatively little is known about the pharmacokinetics of anticancer drugs in the elderly, it is clear that aging influences the disposition of many drugs [2, 3, 5, 7, 16, 22, 29]. Age-related declines in the functional capacity of various organs that are responsible for drug elimination have been implicated in worsened toxicity [3, 17]. Although age is often associated with declines in organ function, alterations in drug disposition do not occur uniformly or exclusively within the older age group. More attention should be focused on identifying the appropriate parameters that better predict drug disposition and toxicity.

For these nine drugs, no significant correlation between drug clearance rate and age has been identified. Many of these drugs are assumed to be eliminated by primarily renal or hepatic processes. Although the elderly are known to have reduced renal and hepatic function [5], unidentified clearance mechanisms may take over as organ functional capacity declines. In addition, if the primary mechanism for elimination of these drugs is hepatic, one would expect a much less dramatic effect than that shown for renally cleared drugs, given the weaker association of age and impaired hepatic function [5].

Table 1. Group characteristics and correlation coefficients for age versus drug and creatinine clearances

Drug	Number of patients	Age (years)			Creatinine clearance (ml/min)			Drug clearance (ml/min)		
		Mean	SD	Range	Mean	SD	Correlation with age	Mean	SD	Correlation with age
Brequinar	51	54.5	11.0	34–74	88.9	32.7	–0.404	2.3	1.1	–0.083
DCMTX	23	57.6	10.3	39–72	86.4	24.7	–0.512	276.0	111.0	–0.222
HMBA, 5-day	10	61.5	10.7	38–72	73.4	16.3	–0.391	136.0	65.5	–0.080
HMBA, 10-day	12	60.1	6.0	49–69	84.0	27.6	0.129	162.0	98.7	0.264
Menogaril	28	54.5	10.3	31–72	82.7	27.4	–0.215	0.6	0.6	–0.188
NMF, intravenous	16	54.3	12.1	29–71	69.1	23.4	–0.291	32.2	16.5	–0.407
NMF, oral	25	56.3	9.2	43–75	96.4	36.8	–0.570	94.2	59.6	–0.007
Piroxantrone	31	55.7	11.2	29–72	77.9	27.6	–0.315	1260.0	481.0	–0.104
Taxol	16	52.7	12.9	38–72	86.9	28.8	–0.381	330.0	258.0	0.053
TMTX, bolus	32	52.8	12.5	21–73	93.5	35.3	–0.561	66.9	42.3	0.019
TMTX, daily × 5	33	55.1	11.1	30–70	84.4	55.1	–0.310	56.2	38.4	0.282
TMTX-organ dysfunction	41	59.6	9.6	36–76	70.2	27.4	–0.509	27.5	15.6	0.075
Topotecan	26	52.7	11.4	35–77	80.1	25.1	–0.381	1220.0	1150.0	–0.044
Totals[a]	344	55.7	11.1	21–77	83.7	31.6	–0.370	1.0	0.6	–0.016

DCMTX, Dichloromethotrexate; HMBA, hexamethylene bisacetamide; NMF, *N*-methylformamide; TMTX, trimetrexate

[a] Drug clearances for each drug were normalized as a ratio to the mean clearance for that drug

Although the patients studied were limited to those with adequate renal function, the results achieved are not due to the selection of elderly patients with unusually good creatinine clearance as demonstrated by the inverse relation between age and creatinine clearance ($r = -0.37$, $P = < 0.0001$; Fig. 2A). Rowe et al. [23] reported a similar significant correlation between the effect of age on creatinine clearance in men ($r = -0.54$).

No evidence of clinician bias in treating older patients was found in these phase I studies with regard to delivered drug doses. The proportion of patients aged over 65 years who received treatment doses at or above the MTD was comparable with that of patients younger than 65 years. In addition, older patients experienced toxicity at rates similar to that of younger patients. Although only a small number of patients older than 75 years were treated, our results suggest that the elderly who meet functional screening criteria for phase I trials do not experience greater toxicity and should not be excluded from phase I trials on the basis of age.

Although our data do not support a significant relation identifying age as a variable predicting altered drug clearance, these were relatively small studies and none of the "oldest old" (patients aged over 80 years) were studied. Other investigators with access to pharmacokinetic data may be capable of identifying similar correlations (or a lack thereof).

As our population ages, more elderly patients will become candidates for chemotherapy trials. These data suggest that patients should not be excluded solely on the basis of age. For this reason, it will be essential to collect information about age, clearance rate, and toxicity prospectively in phase I and phase II trials of new anticancer drugs. With active drugs entering phase II/III studies, relationships between age, clearance rate, and toxicity can more thoroughly be examined.

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