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Toshimichi Miya · Tomoyuki Goya
Osamu Yanagida · Hiroshi Nogami
Yoshihiko Koshiishi · Yasutsuna Sasaki

The influence of relative body weight on toxicity of combination chemotherapy with cisplatin and etoposide

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Abstract *Purpose*: This study was conducted to determine whether there was any relationship between the adverse toxicity of combination chemotherapy and clinical values including age, sex, creatinine clearance (Ccr), body surface area and relative body weight. *Methods*: Cisplatin at a dose of 80 mg/m^2 on day 1 and etoposide at a dose of 100 mg/m^2 on days 1, 2 and 3 were given to 42 consecutive patients with solid tumors. All patients had normal major organ function and received uniform hydration therapy. *Results*: Body Mass Index as a measure of relative body weight was inversely correlated with the percentage decrease in white blood cells ($P = 0.0681$) and platelet count ($P = 0.0115$). Body surface area was also inversely correlated with leukopenia ($P = 0.0171$) and thrombocytopenia ($P = 0.0058$). In contrast, age, sex and Ccr had no significant relationship with adverse toxicity. *Conclusions*: It is concluded that dose adjustment of combination chemotherapy with cisplatin and etoposide according to age or ideal body weight is not appropriate and that a conventional dose modification method based solely on body surface area is probably not sufficient to reduce interpatient variability of cancer chemotherapy. A pharmacokinetic and pharmacodynamic study of combination chemotherapy is warranted to establish the ideal dose modification method.

Key words Body mass index · Interpatient variability · Dose adjustment

T. Miya (✉) · T. Goya · O. Yanagida
H. Nogami · Y. Koshiishi
Department of Surgery II,
Kyorin University School of Medicine,
Shinkawa 6-20-2, Mitaka, Tokyo, 181, Japan
Tel. +81/422/47/5511; Fax +81/422/44/3576

Y. Sasaki
Department of Hematology/Oncology,
National Cancer Center Hospital East,
Kashiwanoha 6-5-1, Kashiwa, Chiba 277, Japan

Introduction

Since the success of an anticancer drug requires control of plasma concentrations within a narrow therapeutic range, close adjustment of doses and meticulous monitoring of adverse effects are essential [9]. Doses of chemotherapeutic agents have been conventionally adjusted according to the body surface area (BSA) [6, 11]. However, this may be of limited value in producing a consistent clinical outcome [13, 22, 24]. Although it is known that several factors such as renal, cardiac and hepatic function affect elimination of a drug, only a few studies have actually dealt with the relationship between physiological function and pharmacokinetics of anticancer drugs [4, 8, 29]. The dose modification method, based on an individual characteristic, remains empirical. It is reported that obesity and age influence the distribution and clearance of some drugs, resulting in interpatient variation in pharmacological behavior [7, 25, 27]. Little information is available concerning the influence of these factors on combination chemotherapy.

The combination chemotherapy of cisplatin and etoposide (PE) is one of the most effective and widely employed cytotoxic treatments of solid tumors including lung cancer. The aim of the current analysis was to determine the relationship between clinical values, including relative body weight, BSA and age, and the adverse toxicity of PE therapy and to assess the conventional dose adjustment method of cancer chemotherapy.

Patients and methods

Patient selection

All of our chemotherapy-naive patients treated by PE therapy from January 1995 through June 1996 were included in the current analysis. Patients eligible for this study had to fulfill the following criteria: age 18 to 78 years, histological or cytological proof of malignant disease, a performance status (PS) of 0–2 on the Eastern Cooperative Oncology Group (ECOG) scale [20], a life expectancy of more than 8 weeks, adequate bone marrow function including

white blood cell count (WBC) $>4000/\mu l$, platelet count (Plt) $>120\ 000/\mu l$ and hemoglobin (Hb) >9 g/dl, renal function (serum creatinine <1.5 mg/dl, creatinine clearance, Ccr >70 ml/min), hepatic function (total protein >6.0 g/dl, serum albumin >3.0 g/dl, GOT and GPT levels less than twice normal range) and cardiac function (normal ECG, no history of congestive heart failure or infarction), and normal levels of serum sodium. Ccr was determined by the 24-h method. Patients who had standard or effective treatment other than PE therapy were excluded from this therapy. Written informed consent was obtained from all patients.

Drug administration schedule

Patients were treated with PE therapy. Cisplatin was injected intravenously at 80 mg/m^2 over 1 h on day 1, and etoposide was given at 100 mg/m^2 over 90 min on days 1, 2 and 3. The chemotherapy dose was based on the BSA calculated from actual body weight and height [6, 11]. All patients received uniform hydration and diuretic treatment. Prehydration involved the infusion of 1 l normal saline. Posthydration involved the infusion of 2.5 l 5% glucose in normal saline with 300 ml 20% mannitol over 6 h. On each of the following 7 days, 2 l 5% glucose in normal saline was administered. Each patient received 16 mg dexamethasone on day 1 and 3 mg granisetron hydrochloride on days 1 and 2 as antiemetic therapy, each drug dissolved in 100 ml normal saline injected intravenously over 30 min. Administration of recombinant human granulocyte colony-stimulating factor (rhG-CSF) was not allowed until grade 4 leukopenia appeared, so the nadir value of WBC obtained was little affected by the use of rhG-CSF.

Toxicity analysis

The adverse drug effects during the first course of PE therapy were analyzed to determine whether a quantitative relationship existed between hematological toxicities and clinical values. Blood samples were collected at least twice a week to monitor for hematological and other toxicities. Percentage decreases in WBC (%ΔWBC), Hb (%ΔHb) and Plt (%ΔPlt) nadirs as compared to the values before treatment were used to evaluate the degree of adverse toxicity. We used the Body Mass Index (BMI) as the measure of relative weight which is calculated from the equation: BMI = weight (kg)/[height (m)]^2 [31]. A BMI of 20 to 24 kg/m^2 is defined as the normal range for Japanese individuals. A BMI of >24 and <20 kg/m^2 are defined as obesity and emaciation, respectively. Nonhematological toxicities according to the ECOG toxicity criteria [20] were also determined.

Statistical analysis

Statistical analysis was performed using the computer program STATVIEW II (Brainpower, Calabasas. Calif.) on a Macintosh personal computer (7100/80AV). Simple linear regression models were calculated by the method of least squares. Multivariate analysis for myelosuppression was carried out using a logistic regression model. The explanatory variables were selected by using a stepwise forward procedure with the entry limit fixed as a significant probability of 95%. $P < 0.05$ was considered statistically significant.

Results

Included in the study were 42 consecutive patients treated with PE therapy. Of the 42 patients, 23 with non-small-cell lung carcinoma and 12 with esophageal carcinoma received PE therapy as neoadjuvant chemotherapy. Seven patients with small-cell lung cancer were treated using standard procedures. Ten patients were considered obese and 12 patients were emaciated according to the BMI classification (Table 1).

Table 1 Patient characteristics (*ECOG* Eastern Cooperative Oncology Group, *NSCLC* non-small-cell lung cancer, *SCLC* small-cell lung cancer)

No. of patients	42
Sex (M/F)	36/6
Age (years)	
Median	61.5
Range	43–77
ECOG performance status	
0/1/2	27/9/6
Disease type	
Lung (NCSLC)	23
Lung (SCLC)	7
Esophagus	12
Body Mass Index	
<20 (emaciated)	12
20–24 (normal)	20
>24 (obese)	10
WBC (/μl)	7869 ± 2357
Plt ($\times 10^4$/μl)	29.6 ± 12.1
Hb (g/dl)	12.8 ± 1.7
Ccr (ml/min)	102.1 ± 27.4
Albumin (g/dl)	3.4 ± 0.4
GOT (IU/l)	24.6 ± 10.1

Table 2 Univariate analysis for myelotoxicity. %ΔWBC = (WBC before treatment − WBC nadir)/WBC before treatment × 100; %ΔPlt and %ΔHb were calculated in the same manner

Factor	%ΔWBC		%ΔPlt		%ΔHb	
	r	*P*-value	*r*	*P*-value	*r*	*P*-value
Age	0.087	0.5821	0.312	0.0442	0.067	0.6743
Sex	0.129	0.4139	0.013	0.9362	0.080	0.6126
PS	0.113	0.4754	0.356	0.0207	0.073	0.6473
BSA	−0.366	0.0170	−0.419	0.0058	−0.111	0.4854
BMI	−0.284	0.0681	−0.386	0.0115	−0.288	0.0643
Ccr	−0.123	0.4359	−0.045	0.7753	−0.129	0.4160
Albumin	−0.087	0.5852	−0.155	0.3275	−0.123	0.4384
GOT	0.200	0.2039	0.113	0.4762	0.071	0.6555

The mean WBC, Plt and Hb levels before treatment were 7869 ± 2357/μl, 29.6 ± 12.1 × 10^4/μl and 12.8 ± 1.7 g/dl, respectively. The mean WBC, Plt and Hb nadirs were 2187 ± 1057/μl, 11.5 ± 6.5 × 10^4/μl and 10.2 ± 1.7 g/dl, respectively. The relationships between the clinical baseline features and hematological toxicity of PE therapy analyzed by the simple regression model are summarized in Table 2. Of eight variables evaluated, the degree of thrombocytopenia was significantly correlated with a smaller BSA ($P = 0.0058$), BMI ($P = 0.0115$) and a poorer PS ($P = 0.0207$). The BSA was also correlated inversely with the degree of leukocytopenia ($P = 0.017$). There was a tendency for BMI to be inversely correlated with the leukocytopenia ($P = 0.068$).

The relationships between BMI and BSA and hematological toxicity are shown in Figs. 1 and 2. After PE therapy was performed, Ccr moderately decreased to 84.5 from 102.1 ml/min but a correlation between nephrotoxicity and clinical values, BMI and BSA was

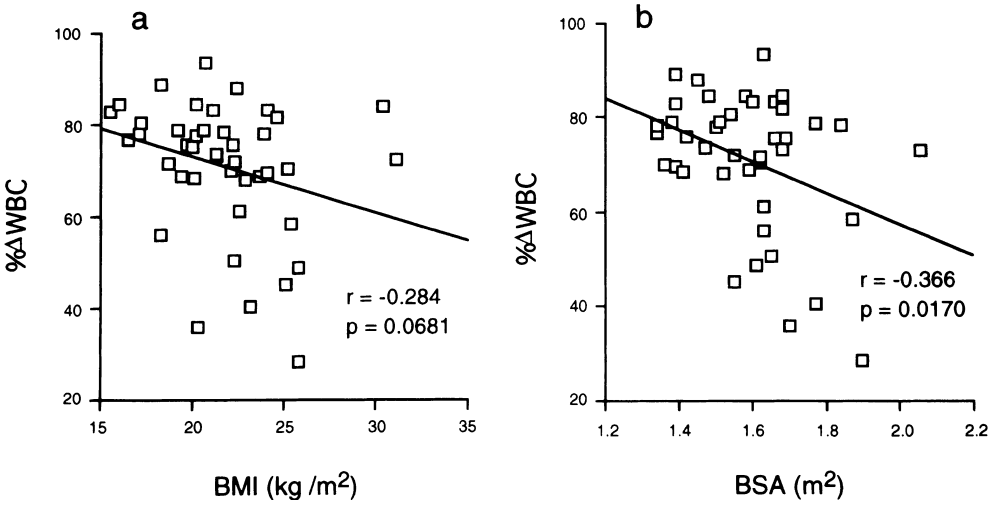

Fig. 1a,b Relationships between BMI (**a**) and BSA (**b**) and leukocytopenia of PE therapy as indicated by changes in WBC count. BMI tended to be correlated inversely with the degree of leukocytopenia ($P = 0.068$), and BSA was significantly correlated inversely with the degree of leukocytopenia ($P = 0.017$)

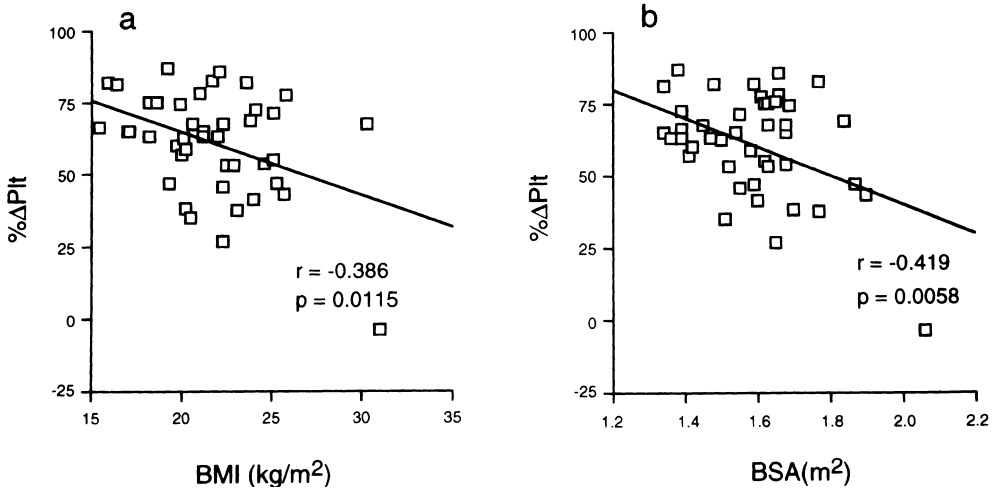

Fig. 2a,b Relationships between BMI (**a**) and BSA (**b**) and thrombocytopenia of PE therapy as indicated by changes in platelet count. Both BMI and BSA were significantly correlated inversely with the degree of the thrombocytopenia ($P = 0.0115$ and 0.0058, respectively)

not found. No other significant correlation was found between hematological toxicity and clinical features including age, sex, GOT and albumin concentration.

Multivariate regression analysis was carried out to clarify the relationship between myelotoxicity and a number of demographic parameters (Table 3). The only significant independent predictor of leukocytopenia obtained by the step regression method was BSA. The best fitting model with significant independent predictors for thrombocytopenia included BMI and PS ($R^2 = 0.298$)

Nonhematological toxicities such as nausea, diarrhea and stomatitis were also examined for a correlation with clinical values but no significant relationship was observed among these factors (data not shown).

Table 3 Stepwise and logistic regression of myelotoxicity

	Factor	Coefficient	SE	*P*-value
%ΔWBC	BSA	−0.366	0.133	0.017
	The overall R^2 value for the model was 0.134			
%ΔPlt	BMI	−0.0218	0.008	0.0041
	PS	0.0840	0.003	0.0144
	The overall R^2 value for the model was 0.289			

Discussion

Scientific and reasonable approaches to establish the optimum method of administering an anticancer drug should be based on information from clinical pharmacology. It has been reported that the pharmacokinetics of cisplatin and etoposide have significant interpatient variability and that this variability is correlated with toxicity [2, 16, 23]. Only a few studies have actually demonstrated the dose modification method established by pharmacological approaches according to individual major organ function [4, 8, 28]. The influence of other minor factors such as age, gender and fat volume remains unclear. It is tempting to assume that these factors may have a significant influence on pharmacokinetics of chemotherapy resulting in the interpatient variability of toxicity because there is a wide interpatient variability of pharmacokinetics even in patients with normal organ function [19, 32].

It has been proposed that toxicity of chemotherapy tends to be severe in obese patients because a lipid-insoluble drug is distributed poorly in adipose tissue with

the result that obese patients theoretically receive a relative overdose if the dose is based on actual body weight [5]. However, little clinical data exist to support this proposal. It has been reported that the elimination half-lives of some anticancer drugs including doxorubicin [25], cyclophosphamide [21] and ifosfamide [17] are prolonged in obese patients depending on body weight. The authors hypothesized that the reduced clearance is due to the relatively decreased activity of cytochrome p-450 enzymes in obese patients [21, 25]. However, increased toxicity associated with increased body weight has not been reported. In contrast, Fleming et al. [10] have suggested that obese patients may require a larger dose of methotrexate to achieve serum concentrations similar to those in lean patients because of the increased glomerular filtration rate in obese individuals. The important practical question raised by these studies is whether the pharmacological findings on obesity are clinically significant. Georgiadis et al. [12] analyzed the chemotherapeutic results in patients with small-cell lung cancer and found no association between obesity and increased toxicity.

In recent phase I studies using similar administration schedules, the recommended dose of paclitaxel has been found to be 350 mg/m^2 in children [14] and 250 mg/m^2 in adults [30]. The traditional interpretation of this phenomenon is that children have better tolerance of chemotherapy and therefore can stand a higher dose [13]. However, children could be relatively underdosed if BSA is used in the calculation of the dose. This is in good agreement with the present findings that BMI and BSA are inversely correlated with toxicity of PE therapy. It has been shown that ideal body weight instead of actual body weight should be used for dose adjustments to obtain consistent serum concentrations of some drugs [1]. We think this management is not appropriate in PE therapy because the lower dose of drugs would have been administered to obese patients who experienced less toxicity in the present study if the adjustment had been based on ideal body weight. These results imply that the dose modification method calculated from actual or ideal body weight is not sufficient and needs to be reassessed.

The influence of age on the pharmacokinetics of cancer chemotherapy has been reported [19, 32]. We have found that the area under the concentration curve (AUC) of CPT-11 is related to patient age but that age is not a significant variable for adverse toxicity [26]. The intensity of taxol for ovarian cancer has also been reported not to be affected by age [3]. It is reasonable to consider that age-related physiologic changes such as decreases in renal function as well as hepatic enzyme activity and hepatic blood flow may account for the reduced elimination of certain drugs in the elderly population. In the present study, all patients had normal organ function regardless of age and no evident correlation was observed between age and toxicity of PE therapy. Because patients who fulfilled the criteria of age under 78 years were evaluated in this study, we could not draw any conclusion concerning the influence of greater age (patients aged over 80 years) on drug toxicity.

Gurney has reviewed the method of dose calculation of anticancer drugs and has found no relationship between BSA and pharmacokinetic parameters [13]. He has proposed a non-BSA-based dose calculation method that involves three mandatory steps: prime dose, modified dose and toxicity-adjusted dose (PMT dosing). Another attractive approach for modeling interpatient pharmacological variability is the adaptive control method [15, 18, 22]. Ratain et al. have developed adaptive control dosing of etoposide and have demonstrated individualized dosing based on a pharmacokinetic-pharmacodynamic model allowing higher dose intensity without increasing the risk of life-threatening toxicity [22]. However, one of the obstacles to introducing therapeutic drug monitoring into routine clinical practice is the financial cost and inconvenience. In addition, current clinical standards of anticancer treatment, which demand combination chemotherapy, confound such approaches. The influence of obesity on the outcome of combination chemotherapy should be investigated.

Reece et al. have reported that Ccr is a poor predictor of cisplatin disposition and that the peak plasma level and the AUC are significantly correlated with the decline in Ccr after four courses of cisplatin therapy [23]. In the present analysis, most of the patients received only two courses of chemotherapy in a neoadjuvant setting. There was a mild decrease in Ccr after chemotherapy and no significant correlation was found between nephrotoxicity and BSA, BMI or various physiologic parameters.

In conclusion, although the influence of fat volume on pharmacological behavior of cancer chemotherapy is minimal, the trend was evident. The impact of obesity or emaciation on chemotherapy should be taken into consideration and the conventional dose modification method based solely on BSA is probably not sufficient to reduce interpatient variability. Dose adjustments of PE therapy based on age and ideal body weight are also not supported by the results of this study. Pharmacokinetic and pharmacodynamic study, not only for single agents but also for combination chemotherapy including the investigation of drug-drug interaction, is warranted to establish the ideal dose modification method.

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References

1. Abernathy DR, Greenblatt DJ, Smith TW (1981) Digoxin disposition in obesity: clinical pharmacokinetic investigation. Am Heart J 102: 740
2. Arbuck SB, Douglass HO, Crom WR et al (1986) Etoposide pharmacokinetics in patients with normal and abnormal organ functions. J Clin Oncol 11: 1690

3. Bicher A, Sarosy G, Kohn E, Adamo D, Davis P, Jacob J, Chabner BC, Reed E (1993) Age does not influence taxol dose intensity in recurrent carcinoma of the ovary. Cancer 71: 594
4. Chatelut E, Canal P, Brunner V, Chevreau C, Pujol A, Boneu A, Roche H, Georges H, Bugat R (1995) Prediction of carboplatin clearance from standard morphological and biological patient characteristics. J Natl Cancer Inst 87: 575
5. Cheymol G (1988) Drug pharmacokinetics in the obese. Fundam Clin Pharmacol 2: 239
6. Du Bois D, Du Bois EF (1916) A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 17: 863
7. Egorin MJ (1993) Cancer chemotherapy in the elderly. Semin Oncol 20: 43
8. Egorin MJ, Van Echo DA, Tipping SJ, Olman EA, Whitacre MY, Thompson BW, Aisher J (1984) Pharmacokinetics and dosage reduction of *cis*-diammine(1,1-cyclobutanedicarboxylato) platinum in patients with impaired renal function. Cancer Res 44: 5432
9. Evans WJ, Relling V (1989) Clinical pharmacokinetics-pharmacodynamics of anticancer drugs. Clin Pharmacokinet 16: 327
10. Fleming RA, Eldridge RM, Johnson CE, Stewart CF (1991) Disposition of high-dose methotrexate in an obese cancer patient. Cancer 68: 1247
11. Gehan EA, George SL (1970) Estimation of human body surface area from height and weight. Cancer Chemother Rep 54: 225
12. Georgiadis MS, Steinberg SM, Hankins JA, Ihde DC, Johnson BE (1995) Obesity and therapy-related toxicity in patients treated for small-cell lung cancer. J Natl Cancer Inst 87: 361
13. Gurney H (1996) Dose calculation of anticancer drugs: a review of current practice and introduction of an alternative. J Clin Oncol 14: 2590
14. Hurwitz CA, Relling MV, Weitmann SD, Ravindranath Y, Vietti T, Strother DR, Ragab AH, Pratt C (1993) Phase I trial of paclitaxel in children with refractory solid tumors: a Pediatric Oncology Group study. J Clin Oncol 11: 2324
15. Jodrell DI, Reyno LM, Sridhara R, Eisenberger MA, Tkaczuk KH, Zuhowski EG, Sinibaldi VJ, Novak MJ, Egorin MJ (1994) Suramin: development of a population pharmacokinetic model and its use with intermittent short infusion to control plasma drug concentration in patients with prostate cancer. J Clin Oncol 12: 166
16. Joel SP, Shah R, Sleivin ML (1994) Etoposide dosage and pharmacodynamics. Cancer Chemother Pharmacol 34 [Suppl]: S69
17. Lind MJ, Margison JM, Cerny T, Thatcher N, Wilkinson PM (1989) Prolongation of ifosfamide elimination half-life in obese patients due to altered drug distribution. Cancer Chemother Pharmacol 25: 139
18. Mick R, Ratain MJ (1991) Modeling interpatient pharmacodynamic variability of etoposide. J Natl Cancer Inst 83: 1560
19. Miya T, Sasaki Y, Karato A, Saijo N (1992) Pharmacokinetic study of mitomycin C with emphasis on the influence of aging. Jpn J Cancer Res 83: 1382
20. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, MacFradden ET, Carbone PP (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5: 649
21. Powis G, Reece P, Ahmann DL, Ingle JN (1987) Effect of body weight on the pharmacokinetics of cyclophosphamide in breast cancer patients. Cancer Chemother Pharmacol 20: 219
22. Ratain MJ, Mick R, Schilsky RL, Vogelzang NJ, Berezin F (1991) Pharmacologically based dosing of etoposide: a means of safely increasing dose intensity. J Clin Oncol 9: 1480
23. Reece PA, Stafford I, Russel J, Khan M, Gill PG (1987) Creatinine clearance as a predictor of ultrafilterable platinum disposition in cancer patients treated with cisplatin: relationship between peak ultrafilterable platinum levels and nephrotoxicity. J Clin Oncol 5: 304
24. Reilly JJ, Workman P (1994) Is body composition an important variable in the pharmacokinetics of anticancer drugs? Cancer Chemother Pharmacol 34: 3
25. Rodvold KA, Rushing DA, Tewksbury DA (1988) Doxorubicin clearance in the obese. J Clin Oncol 6: 1321
26. Sasaki Y, Hakusui H, Mizuno S, Morita M, Miya T, Eguchi K, Shinkai T, Tamura T, Ohe Y, Saijo N (1995) A pharmacokinetic and pharmacodynamic analysis of CPT-11 and its active metabolite SN-38. Jpn J Cancer Res 86: 101
27. Stein BN, Petrelli NJ, Douglas HO, Driscoll DL, Arcangeli G, Meropol NJ (1995) Age and sex are independent predictors of 5-fluorouracil toxicity. Cancer 75: 11
28. Stewart CF (1994) Use of etoposide in patients with organ dysfunction: pharmacokinetic and pharmacodynamic considerations. Cancer Chemother Pharmacol 34 [Suppl]: S76
29. Twelves CJ, Dobbs NA, Michael Y, Summers LA, Gregory W, Harper PG, Rubens RD, Richards MA (1992) Clinical pharmacokinetics of epirubicine: the importance of liver biochemistry test. Br J Cancer 66: 765
30. Wiernik PH, Schwartz EL, Einzig A, Strauman JJ, Lipton RB, Dutcher JP (1987) Phase I trial of Taxol given as a 24-hour infusion every 21 days: response observed in metastatic melanoma. J Clin Oncol 5: 1232
31. Williamson DF (1993) Descriptive epidemiology of body weight and weight change in U.S. adults. Ann Intern Med 119: 646
32. Yamamoto N, Tamura T, Maeda M, Ando M, Shinkai T, Eguchi K, Ohe Y, Oshita F, Shiraishi J, Katsumata N, Saijo N (1995) The influence of ageing on cisplatin pharmacokinetics in lung cancer patients with normal organ function. Cancer Chemother Pharmacol 36: 102