Review Article

Inter-Ethnic Differences—How Important is it in Cancer Treatment?

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Abstract

It is now well recognised that there are inter-ethnic differences accounting for variations in both pharmacokinetics (PK) and pharmacodynamics (PD) of drugs, resulting in differences in drug responses. Treating physicians should be aware of pharmacogenetic differences that may exist between the races while extrapolating data generated from other populations to their own patients in order to ensure optimal treatment response and minimise toxicity. This is especially crucial in the practice of oncology where many anti-cancer drugs have narrow therapeutic indices. This paper discusses some commonly used drugs in cancer treatment where inter-ethnic differences in drug safety and efficacy are known to exist that are relevant to the Asian physician.

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Introduction

Inter-individual differences in drug responses are well recognised and may be due to genetic or environmental differences. These genetic or environmental influences may also result in inter-ethnic or inter-geographic differences in drug response. Indeed, drug regulatory authorities are beginning to acknowledge these differences. For example, in 1999, the United States Food and Drug Administration (FDA) recognised that drugs may be ethnically sensitive and advocated bridging studies for extrapolating clinical trial results from one region to another.[1] At that time, they recommended collection of race and ethnicity information in clinical trials for the 3 main races: Caucasian, Black and Asian. In its updated document in 2005, the drug authority recognised the need to extend this race category further to include 5 minimum ethnic groups, namely, Caucasian, Black/African-American, Asian, American Indian/Alaska Native, and Native Hawaiian/other Pacific Islander.[2]

In August 2005, the United States FDA approved its first race specific drug, Bidil, a combination drug of hydralazine and isosorbide nitrate, for the treatment of congestive cardiac failure specifically in black patients, based on the study by Taylor et al.[3] Approval of race specific drugs, however, is an issue fraught with controversies. Many would argue that, strictly speaking, race is not a scientific classification but a social concept, and that racial categorisation may simply be a surrogate marker of genetic and other biological determinants.[4] Moreover, inter-breeding has resulted in sharing of genetic materials between different populations, such that self identification of race may be challenging. For example, in the United States year 2000 census, almost 7 million people identified themselves as belonging to more than one race, and 800,000 responders claimed they were both black and white.[5] Furthermore, the effect of a drug is usually not an "all or none" phenomenon, and a 'race specific drug' that works particularly well in one ethnic population may be equally effective in other ethnic groups.

As physicians in Asia, it is particularly pertinent to appreciate inter-ethnic differences in drug disposition as data is often extrapolated from landmark studies generated from Caucasian patients to Asian populations for clinical use, which may not be relevant for some drugs. Moreover, Western studies that include Asian patients tend to consider

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'Asians' as a homogeneous population, when in reality, Asia comprises many heterogeneous populations of people that may have physical and biological differences that influence drug disposition. Here, we discuss some commonly used drugs in cancer treatment where inter-ethnic differences in drug safety and efficacy are known to exist that are relevant to the Asian physician.

Warfarin

Warfarin, a commonly used oral anti-coagulant worldwide, has been available since the 1950s, and is frequently used for the prevention or treatment of thromboembolism in cancer patients. It has a narrow therapeutic index, and wide inter-individual variation in dose requirements is well described. There is also evidence to show that there are inter-ethnic differences in warfarin dose requirements. Blann et al[6] compared warfarin requirements of 3 races: Caucasians, Asians and Afro-Carribeans, and observed that Afro-Carribeans required the highest maintenance warfarin dose amongst the 3 groups. Similarly, Dang et al[7] showed in their study that warfarin requirement is highest amongst Afro-Americans, intermediate in Caucasians and lowest amongst Asians; the mean maintenance warfarin dose for Afro-American patients was 6.1 mg compared to 5.1 mg and 3.4 mg for Caucasian American and Asian American patients respectively. Consistent with the study by Dang et al, a Hong Kong study by Yu et al[8] also reported that the mean warfarin dose for Hong Kong Chinese patients was 3.3 mg.

Apart from differences in warfarin dose requirements between the 3 major races in the world, there is reported difference in warfarin requirements even between different ethnic groups within Asia.[9] We previously compared warfarin requirements amongst 275 Singapore Chinese, Malay and Indian patients, and noted that Indians required almost 2 times the maintenance warfarin dose (5.9 mg) compared to Chinese (3.5 mg) and Malays (3.6 mg); these differences persisted even after adjusting for body weight, where Indians required 0.089 mg/kg body weight daily, compared to 0.058 mg/kg/day and 0.059 mg/kg/day for Chinese and Malays respectively.[10] It is now known that inter-ethnic difference in warfarin dose requirements is due to variants in the gene encoding Vitamin K epoxide reductase complex 1 (*VKORC1*). *VKORC1*, the target enzyme of warfarin, recycles vitamin K 2, 3 epoxide back to active vitamin K hydroquinone, a vital co-factor in the activation of vitamin K dependant clotting factors. In their 2005 landmark paper, Rieder et al[11] comprehensively sequenced the *VKORC1* gene including the non-coding regions and identified 10 common intronic single nucleotide polymorphisms (SNPs). Combination of these SNPs resulted in the identification of common *VKORC1* haplotypes that were associated with warfarin dose requirement (H1 through H9). Haplotypes H1 and H2 were associated with low warfarin requirement (2.9 and 3.0 mg per day), while individuals with haplotypes H7, H8 and/or H9 required higher doses of warfarin (5.0 to 6.0 mg per day). These haplotypes correlated with liver VKOR mRNA expression levels, suggesting that these genetic variants have biological significance. Interestingly, inter-ethnic differences in the frequency distribution of these *VKORC1* haplotypes exist amongst the 3 major races. Asians predominantly carry the low warfarin requiring haplotypes, H1 and H2, while the high warfarin requiring haplotypes, H7, H8 and H9, are more common amongst Africans and Caucasians but rare in Asians.[10] In the Singaporean population, there is also significant difference in frequency distribution of *VKORC1* haplotypes between Chinese, Malays and Indians. Seventy-four percent of Chinese were homozygous for the H1 haplotype, a low warfarin-requiring haplotype; in contrast, 79% of Indians carried 2 copies of a high warfarin requiring haplotype, H7, H8 or H9.[10] These genotype differences could explain why Chinese require lower doses of warfarin than Indians. Malays, on the other hand, have intermediate genotype between Chinese and Indians. In the absence of genetic information, race was an important predictor of warfarin dosage in the Singapore population. Together with clinical factors such as age and weight, a model may be created that accounted for about 50% of the variability in warfarin requirement. However, when genetic information is included, race is no longer important as a predictive factor, suggesting that while race is a useful surrogate of the *VKORC1* genotype, actual genotyping is more accurate as a predictor of warfarin requirement than a surrogate marker, i.e. race.[11] Furthermore, although the *VKOR* genotype of Malays is intermediate between Chinese and Indians, the warfarin dose requirements of Malays is similar to that of Chinese (3.5 mg vs 3.6 mg per day), suggesting that there must be other genetic and environmental factors influencing warfarin dosing in Malays that warrant further evaluation.

Doxorubicin

Doxorubicin, an anthracycline antibiotic with wide spectrum cytotoxic activity, has been used in cancer therapy for decades, especially in the treatment of breast cancer and lymphoma. Its main toxicities include myelosuppression, emesis and cumulative cardiac toxicity which are often dose limiting. Apart from inter-individual pharmacokinetic and pharmocodynamic variability, there is also data to suggest inter-ethnic differences, with Asians being more susceptible to doxorubicin-induced myelosupression compared to Caucasians.[12,13]

In 2002, Ma et al[12] published a retrospective study comparing Hong Kong Chinese breast cancer patients

treated with standard dose adjuvant doxorubicin and cyclophosphamide (n = 85), versus a large group of Caucasian patients treated on a National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol (n = 1462). Significant inter-ethnic difference was observed in chemotherapy-induced haematologic-toxicities, with more than 75% of Chinese patients developing grade 3 or 4 neutropaenia overall compared to fewer than 5% of Caucasian patients. A similar difference was reported by our group several years ago in a prospective study comparing Chinese versus Caucasian breast cancer patients receiving standard dose adjuvant doxorubicin and cyclophosphamide. More than half of the Chinese patients developed grade 4 neutropaenia compared to fewer than 20% of Caucasian patients.[13] Apart from these observed differences between Asians and Caucasian, there are also possible inter-ethnic variability between Asian races. Our study on 99 breast cancer patients treated with single agent doxorubicin showed that Chinese experienced the greatest degree of neutrophil suppression, Malays to be intermediate, while Indians experienced the least neutrophil suppression.[14]

The doxorubicin disposition pathway is complex, and many candidate genes have been studied in an attempt to elucidate the pharmacogenetic mechanisms for the observed inter-ethnic difference in doxorubicin-induced toxicity, including *ABCB1, CYP3A5*3, CBR1* and 3 orphan nuclear receptors, CAR, PAR, HNF4α, that regulate the expression of CYP3A4. Disappointingly, none of these genes was found to correlate with doxorubicin pharmacokinetics and pharmacodynamics.[15] More recently however, there is evidence to suggest that polymorphisms in the gene that encodes for the enzyme *CBR3* which metabolizes doxorubicin to doxorubicinol, a metabolite that has one tenth the activity of doxorubicin, may account for inter-individual as well as inter-ethnic variability in doxorubicin metabolism. Lu et al[16] described a common *CBR3* variant, *11G>A*, that influenced doxorubicin pharmacokinetics and pharmocodynamics. Patients who were homozygous for the *CBR3 11A* allele have lower area under the concentration-time curve (AUC) ratio of doxorubicinol to doxorubicin, implying that these patients were less efficient in converting doxorubicin to doxorubicinol, thus accumulating more doxorubicin in their blood. In concordance, these patients experienced greater degree of neutrophil and platelet suppression, but better tumour response. Interestingly, there is significant inter-ethnic difference in *CBR3 11G>A* genotype distribution, with the A allele, which is associated with greater doxorubicin induced toxicity, being found more commonly amongst Chinese, compared to Indians and Caucasians.[16] This observation could at least in part explain some of the inter-ethnic difference in doxorubicin toxicities observed between the different populations.

Docetaxel

Docetaxel, a broad spectrum taxane which exerts its anti-tumour effect by binding to and promoting stabilisation of the microtubule network, is commonly used in the treatment of a variety of solid tumours such as lung, breast, gastric, ovarian and prostate cancer. The main side effects of docetaxel are myelosuppression and peripheral neuropathy. In 2003, Millward et al[17] published one of the first prospective studies which demonstrated inter-ethnic difference in tolerance to docetaxel. In this study, Chinese patients in Singapore and Caucasian patients in Australia with stage IIIB and IV non small cell lung cancer were treated with first line combination chemotherapy with three weekly docetaxel 75 mg/m^2 and carboplatin (area under the plasma concentration time curve [AUC] of 6). While the first 6 Caucasian patients tolerated the treatment well, 3 out of the first 6 Chinese patients enrolled developed febrile neutropaenia requiring hospitalisation and one died from neutropaenic sepsis. These toxicities prompted a protocol amendment at the Singapore site to reduce the carboplatin dose to AUC of 4.5. The final analysis showed that the mean cycle 1 neutrophil count was lower in the Asian group (0.67x10^9/L at carboplatin AUC of 6, n = 6; 0.99x10^9/L at carboplatin AUC of 4.5, n = 15) compared to the Caucasian cohort (1.04x10^9/L at carboplatin AUC of 6, n = 43), even though the Asian cohort received lower drug doses overall following the protocol amendment. However, the Asian group had better tumour response rate that was almost twice that of the Caucasian patients (65% vs 31%, $P = 0.01$), and multivariate analysis showed that ethnicity was one of the most important predictors of treatment response in this study.

Of interest to note are the different docetaxel doses that are commonly administered in different geographic populations. In Caucasians, the common starting dose of first line single agent docetaxel is 100 mg/m^2,[18,19] while in Asian countries such as China and Korea, the common starting dose is 70 to 75mg/m^2,[20] in Japan, the approved starting dose for docetaxel is 60 mg/m^2.[21] Yet, despite these reduced doses, Asians have higher reported febrile neutropaenia rates compared to Caucasians.[18-21] A possible explanation for this inter-ethnic difference in docetaxel tolerance lies with the difference in docetaxel clearance between races.[22] Goh et al[23] showed that docetaxel clearance is approximately 40% lower while drug exposure (docetaxel AUC) is approximately 25% higher in Asians compared to Caucasians. Unfortunately, although many pharmacogenetic studies have been conducted that examined various implicated genes, including *ABCB1, CYP3A4, CYP3A5, PXR*, and *CAR*, the genetic reason for the inter-ethnic difference in docetaxel metabolism is still not forthcoming. Indeed, Marsh et al[24] studied 27 SNPs in 16 candidate genes in a large cohort of ovarian cancer

patients treated with docetaxel or paclitaxel and carboplatin (n = 914) and found no correlation between any of these genetics variants with treatment outcomes or toxicities. Hence, for docetaxel, the search is still on for the mechanism underlying the inter-ethnic differences in drug tolerance.

5-Flurouracil (5-Fu)

5-FU, a pyrimidine anti-metabolite, is one of the most active single agents for the treatment of colorectal cancer. It also has activity in a variety of other cancers, including gastric, breast as well as head and neck cancer. 5-FU is metabolised to its inactive form, 5, 6-dihydro-5-fluorouracil, by dihydropyrimidine dehydrogenase (DPYD). The hypothesis that there are regional differences in 5-FU tolerability was tested by Haller et al[25] who conducted a retrospective analysis of safety data from a phase III randomized adjuvant clinical trial comparing 2 different 5-FU containing chemotherapy regimens (5-FU/leucovorin vs capecitabine/oxaliplatin). Of the 2000 or so patients, 10% was Asians. Using Asians as the reference, Haller reported that American and European Caucasians had 2 to 3 fold higher risk of developing grade 3 or 4 gastrointestinal toxicities compared to Asians, suggesting that Asians could tolerate 5-FU better. A number of studies are ongoing to determine the genetic reason for this inter-ethnic difference. One of the implicated genes that have generated much interest is the thymidylate synthase (TYMS) gene which contains 7 exons and a 5′-flanking untranslated enhancer region containing a 28-bp tandem repeat sequence. The number of tandem repeats varies from two (2R) to nine (9R) copies. Variants in the enhancer region of TYMS have been shown to affect thymidylate expression level and hence affect outcome to 5-FU.[26] Interestingly, there is significant inter-ethnic variation in TYMS gene where most Caucasians carry the 2R/2R variant, with only one-third having the 3R/3R variant; in contrast, the 3R/3R variants are 2 times more common in Asians.[26] Based on this observation, a Phase I study of genotype-guided dosing of oral 5-FU-capecitabine is currently being carried out at our centre, and preliminary results showed that Asian patients with the 3R/3R genotype could tolerate 20% higher doses of capecitabine than the current approved dose with minimal dose limiting toxicities.

Gefitinib

Gefitinib, a selective inhibitor of epidermal growth factor receptor (EGFR) intracellular tyrosine kinase domain, has generated much excitement in the treatment of non small cell lung cancer. It is a striking example of a race specific drug where there is significant inter-ethnic difference in terms of drug response and survival rate, with Asian patients faring much better than Caucasians.[27] The molecular predictor for response to gefitinib is the presence of activating mutations in the EGFR tyrosine kinase domain, which are present more commonly in Asian non small cell lung cancer patients than Caucasians.[28] Apart from tumour response, there is also inter-ethnic difference in gefitinib-induced toxicity. Gefitinib-induced intersititial pneumonitis was first reported in a Japanese patient,[29] and it is now apparent that Japanese are several times more susceptible to gefitinib-induced intersititial pneumonitis where the incidence is reported to be about 1.7% among approximately 17,500 Japanese patients treated compared to 0.3% in approximately 56,000 non-Japanese (including Asian and non-Asian) patients treated.[30] The reason underlying this difference is not yet known, but is believed to be due to a separate mechanism from EGFR mutations, as interstitial pneumonitis occurred more frequently in male smokers and in patients whose tumours do not harbor EGFR mutations.

Tamoxifen

Tamoxifen, a selective estrogen receptor modulator, has been approved since the 1970s for the treatment of estrogen receptor-positive breast cancer. It has a complex metabolic pathway, including metabolism via the cytochrome P450 (CYP) pathway to several metabolites. The enzyme CYP2D6 is involved in the conversion of tamoxifen to endoxifen, the most potent metabolite. At least 88 allelic variants of *CYP2D6* have been described, many of which are non-functional or have reduced catalytic activity, resulting in a tetra-modal distribution in metabolizer phenotype: poor, intermediate, extensive and ultra-rapid metabolizer.[31]

Interestingly from an inter-ethnic point of view, there are striking variations in the distribution of *CYP2D6* genetic variants amongst the different populations. *CYD2D6*4* genotype, a common non-functional variant that results in the poor metabolizer phenotype has predominance in the Caucasian population, but is rare in Asians. In contrast, *CYP2D6*10* and *CYP2D6*17* genotypes, which result in the intermediate metabolizer phenotype, are common in the Asian and African populations respectively, but are relatively rare in Caucasian. On the other end of the spectrum are ultra-rapid metabolizers who carry gene duplications or multiple duplications of functional alleles resulting in increased enzyme activity. These genotypes are rare in Caucasians and Asians but occur in 14% of Ethiopians and 2% to 5% of some African populations.[32]

As the metabolism of tamoxifen by CYP2D6 is an activating step, a poor metabolizer will not be able to activate tamoxifen as effectively and hence treatment outcome may be compromised. In a landmark study on tamoxifen pharmacogenetics, Goetz et al[33] reported that breast

cancer patients who were homozygous for the *CYP2D6*4* variant, the predominant variant in Caucasians, have poorer disease-free survival when treated with tamoxifen. In a similar study, Lim et al[34] examined the *CYP2D6*10* variant in the Korean population and found that patients who were homozygous for this genotype had lower level of endoxifen and derived less benefit from tamoxifen therapy. As CYP2D6 metabolizes many commonly used drugs, this inter-population difference in *CYP2D6* genetic variants may have wider clinical implications for other drugs in common use, such as anti-psychotics, tricyclic anti-depressants, and some antiarrhythmics.

Limitations of Current Studies

While much research has been done in pharmacogenetics in recent years, most studies are retrospective and are limited by small sample size. In addition, there have been very few cross-ethnic studies that prospectively compared inter-ethnic differences in drug effects or their influence by ethnic-specific gene variants. Most current studies have adopted a candidate gene approach and focused on single or small number of pathway-specific genetic variants. Advanced genotyping technologies, such as whole genome and next-generation sequencing capabilities, offers the opportunity for an unbiased approach to uncover panels of gene variants that interact to influence drug outcomes in different ethnic groups, and may enhance the development of pharmacogenetic tests that may be applied in clinical practice.

Table 1. Inter-ethnic Difference in Drug Response and Implicated Genes

Drug	Clinical Effects	Implicated Gene
Warfarin	Asians require lower dose.	*VKORC1*
Doxorubicin	Asians experience more myelosuppression.	*CBR3*
Docetaxel	Asians have reduced clearance and experience more myelosuppression.	-
5-Fluoropyrimidines	Asians are less likely to have gastrointestinal toxicities.	*TYMS* (possible role)
Gefitinib	Asians are more likely to have treatment response. Japanese are more susceptible to develop interstitial pneumonitis.	EGFR activating mutations
Tamoxifen		*CYP2D6* (inter-ethnic difference in metabolizer genotypes and phenotypes)

Conclusion

Different populations or ethnic groups are likely to be more similar to each other than they are different. However, differences in disposition of some drugs between races do exist and may be due to genetic or other influences, and several of such examples that are relevant to the Asian patients are illustrated here (Table 1). For example, Asians require lower doses of warfarin, experience more myelosuppression in response to doxorubicin and docetaxel, but are able to tolerate higher doses of 5-FU with less gastrointestinal toxicities. Asians are also more likely to respond to gefitinib therapy while Japanese patients are more susceptible to gefitinib-induced interstitial pneumonitis. Treating physicians should be aware of these pharmacogenetics differences between the races and tailor therapy to be relevant to their population.

REFERENCES

1. Yasuda SU, Zhang L, Huang SM. The role of ethnicity in variability in response to drugs: focus on clinical pharmacology studies. Clin Pharmacol Ther 2008;84:417-23.
2. U.S Department of Health and Human Services Food and Drug Administration. Guidance for Industry: Collection of race and ethnicity data in clinical trials. Clinical Medical 2005.
3. Taylor A, Ziesche S, Yancy C, Carson P, D'Agostino, Ferdinand K, et al. Combination of isosorbide dinitrate and hydralazine in Blacks with heart failure. N Engl J Med 2004;351:2049-57.
4. Schwartz RS. Racial profiling in medical research. N Engl J Med 2001;344:1392-3.
5. Schmitt E. For 7 million people in census, one race category isn't enough. New York Times; 13 March, 2001.
6. Blann A, Herwitt J, Siddiqui F, Bareford D. Racial background is a determinant of average warfarin dose required to maintain the INR between 2.0 and 3.0. Br J Haematol 1999;107:207-9.
7. Dang MT, Hambleton J, Kayser SR. The influence of ethnicity on warfarin dosage requirement. Ann Pharmacother 2005;39:1008-12.
8. Yu HC, Chan TY, Critchley JA, Woo KS. Factors determining the maintenance warfarin dose in Chinese patients. QJM 1996;89:127-35.
9. Zhao F, Loke C, Rankin S, Guo JY, Lee HS, Wu TS, et al. Novel CYP269 genetic variants in Asian subjects and their influence on maintenance warfarin dose. Clin Pharmacol Ther 2004;76:210-9.
10. Lee SC, Ng SS, Chong PY, Rost S, Guo JY, Yap HL, et al. Interethnic variability of warfarin maintenance requirement is explained by VKORC1 genotype in an Asian population. Clin Pharmacol Ther 2006;79:197-205.
11. Rieder M, Reiner A, Gage B, Nickerson D, Eby C, McLeod HL, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. N Engl J Med 2005;352:2285-93.
12. Ma B, Yeo W, Hui P, Ho WM, Johnson PJ. Acute toxicity of adjuvant doxorubicin and cyclophosphamide for early breast cancer- a retrospective review of Chinese patients and comparison with an historic Western series. Radiother Oncol 2002;62:185-9.
13. Beith JM, Goh BC, Yeo W, Sullivan A, Lim S, Zhong S, et al: Inter-ethnic differences in the myelotoxicity of adriamycin/ cyclophosphamide (AC) or adjuvant breast cancer. Proc American Society of Clinical Oncology 2002;21:abstract 252.
14. Hor SY, Lee SC, Wong CI, Lim YW, Lim RC, Wang LZ, et al. PXR, CAR

and HNF4alpha genotypes and their association with pharmacokinetics and pharmacodynamics of docetaxel and doxorubicin in Asian patients. Pharmacogenomics J 2008;8:139-46.

15. Tham LS, Holford N, Hor SY, Tan T, Wang LZ, Lim RC, et al. Lack of association of single-nucleotide polymorphisms in pregnane X receptor, hepatic nuclear factor 4alpha and constituitive androstane receptor with docetaxel pharmacokinetics. Clin Cancer Res 2007;13:7126-32.
16. Fan L, Goh BC, Wong CI, Sukri N, Lim SE, Tan SH, et al. Genotype of human carbonyl reductase CBR3 correlates with doxorubicin disposition and toxicity. Pharmacogenet Genomics 2008;18:623-31.
17. Millward MJ, Boyer MJ, Lehnert M, Clarke S, Rischin D, Goh BC, et al. Docetaxel and carboplatin is an active regimen in advanced non-small-cell lung cancer: a phase II study in Caucasian and Asian patients. Ann Oncol 2003;14:449-54.
18. Sparano JA, Wang M, Martino S, Jones V, Perez EA, Saphner T. Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med 2008;358:1663-71.
19. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, Alanko T, Kataja V, Asola R, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 2006;354:809-20.
20. Perng RP, Shih JF, Chen YM, Chou KC, Lee YC, Tsai CM. A phase II study of single agent docetaxel chemotherapy for non-small cell lung cancer. Jpn J Clin Oncol 2000;30:429-34.
21. Muruyama R, Nishiwaki Y, Tamura T, Yamanoto N, Tsuboi M, Nakagawa K, et al. Phase III study V-15-13 of gefitinib vs docetaxel in previously treated patients with non small cell lung cancer. J Clin Oncol 2008;26:4244-58.
22. Bruno R, Hille D, Riva A, Huinnink W, Van Oosterom A, Kaye S, et al. Population pharmacokinetics/ pharmacodynamics of docetaxel in Phase II studies in patients with cancer. J Clin Oncol 1998;16:187-96.
23. Goh BC, Lee SC, Wang LZ, F Lu, Guo JY, Lamba J, et al. Explaining interindividual variability of docetaxel pharmacokinetics and pharmacodynamics in Asians through phenotyping and genotyping strategies. J Clin Oncol 2002;20:3683-90.
24. Marsh S, Paul J, King CR, Gifford G, McLeod HL, Brown R. Pharmacogenetic assessment of toxicity and outcome after platinum plus taxane chemotherapy in ovarian cancer: The Scottish Randomised Trial in Ovarian cancer. J Clin Oncol 2007;25:4528-35.
25. Haller D, Cassidy J, Clarke S, Cunningham D, Van Cutsem E, Hoff P, et al. Potential regional differences for the tolerability profiles of Fluropyrimidines. J Clin Oncol 2008;26:2118-23.
26. Marsh S, Collie-Duguid ES, Li T, Liu X, Mcleod HL. Ethnic variation in the thymidylate synthase enhancer region polymorphism among Caucasian and Asian population. Genomics 1999;58:310-2.
27. Jiang H. Overview of gefitinib in non-small cell lung cancer: an Asian perspective. Japanese J Clin Oncol 2009;39:137-50.
28. Shigematsu H, Lin L, Takahashi T, Nomura M, Suzuki M, Wistuba II, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancer. J Natl Cancer Inst 2005;97:339-46.
29. Inoue A, Saijo Y, Maemondo M, Gomi K, Tokue Y, Kimura Y, et al. Severe acute interstitial pneumonia and gefitinib. Lancet 2003;361:137-9.
30. Calvo E, Baselga J. Ethnics differences in response to epidermal growth factor receptor tyrosine kinase inhibitors. J Clin Oncol 2006;24:2158-63.
31. Tan SH, Lee SC, Goh BC. Pharmacogenetics in breast cancer therapy. Clin Cancer Res 2008;14:8027-41.
32. Bradford LD. CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. Pharmacogenomics 2002;3:229-43.
33. Goetz M, Rae J, Suman V, Safgren S, Ames M, Visscher D, et al. Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flushes. J Clin Oncol 2005;23:9312-8.
34. Lim HS, Lee HJ, Lee KS, Lee ES, Jang IJ, Ro JS, et al. Clinical implications of CYP2D6 genotypes predictrive of tamoxifen pharmacokinetics in metastatic breast cancer. J Clin Oncol 2007;25:3837-45.