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SELECTED PHARMACOGENETIC PANEL TEST FOR TOXICITY PREVENTION OF DRUG-DRUG INTERACTIONS BETWEEN HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) AND ANTIBLASTIC CHEMOTHERAPY

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Abstract: *The co-administration of antiretroviral therapy (HAART) and anticancer drugs in oncologic patients HIV-positive, may be related with an increased risk of toxicity resulting to pharmacokinetic and pharmacodynamic interactions mediated by drug-metabolizing enzymes or transporters leading to altered drug exposure.*

Here, we review the late findings on the most appropriate gene variants related to the toxicity in patients receiving HAART and chemotherapy. The purpose of this review is to summarize the existing data on the impact of individual pharmacogenomic profile in order to optimize the clinical management of cancer patients with HIV/AIDS.

Several criteria has been used to select a genotyping panel tests, including cytochrome P (CYP) 450 substrates. Results of allelic status from several validated polymorphism assays, allow the stratification of the patients who are most likely respond to combined treatments. The usefulness and costs of the methods used to detect these polymorphisms will be also taken in consideration.

Genotyping of patients for multidrug response is a promising strategy for cancer treatment and personalized therapy in HIV-patients. Based on the individual genetic profiles, the oncologist will have a new features to make personalized treatment decisions for their patients in order to maximize benefit and minimize toxicity.

Keywords: *Pharmacogenomics HIV, AIDS, Genetic test, Solid cancer, Antiblastic chemotherapy, Efavirenz, Nevirapine , Etravirine, lopinavir.*

INTRODUCTION

Currently, the use of Highly Active Antiretroviral Therapy (HAART) into clinical practice has had a striking impact on the outcome of patients with HIV-related cancer[1]. Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin's disease, invasive anal carcinoma, lung carcinoma, skin cancer, colon-rectal cancer and hepatocarcinoma are the most frequent cancers among people with HIV/AIDS[2-5]. However, careful attention must be directed toward the cross toxicity and the possible pharmacokinetic and pharmacodynamic interactions between antiretroviral and Antiblastic Chemoterapy (AC)[6]. Antiblastic treatments produce a significant decrease in CD4 lymphocytes and significantly increase the risk of opportunistic infections (OIs) in patients with HIV-related malignancies[7]. Patients receiving the combination AC plus HAART may achieve better response rates and higher rates of survival than patients who receive AC therapy alone[8].

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For the majority of antiretroviral drugs that are cytochrome P (CYP) 450 substrates, inducers or inhibitors, co-administration with other metabolized drugs could result in drug accumulation and possible toxicity or decreased efficacy of one or both treatments.

Cancer patients receive a large number of drugs during their treatment including those for comorbidity conditions and cancer related syndromes such as pain, emesis, depression, and seizures. However in most cases the consequences are adverse and undesirable, compromising the efficacy of the therapeutic agent or enhancing its toxicity. It has been reported that 20-30% of all adverse drug reactions are caused by the interactions between drugs[9]. Only limited data are available on Drug-Drug Interactions (DDIs) in the treatment of HIV associated malignancies. Protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are substrates and potent inhibitors or inducers of the CYP450 metabolic system. Since many antineoplastic drugs are also metabolized by the CYP450 system, co-administration with HAART could result in either drug accumulation and possible toxicity or decreased efficacy of one or both classes of drugs.

In this fields, inter-individual response could be dependent of the genetic variations associated to HAART-AC administrations. A few examples showing the relationship between single nucleotide polymorphisms (SNPs) in the genes coding for antiretroviral metabolizing enzymes (CYP450s and UGTs) and transporters, and related toxicities are here described.

This paper reviews the potential interactions and subsequent clinical considerations between HAART and the most common AC used in the treatment of HIV-positive cancer patients.

Several antiretrovirals as atazanavir or indinavir are associated with unconjugated hyperbilirubinemia secondary to UGT1A1 inhibition similar to that occurring in Gilbert's syndrome. On the other hand, NRTI as didanosine, stavudine and zidovudine may produce steatosis and it should be stopped or replaced before beginning AC in presence of severe hepatotoxicity. NRTIs as abacavir, emtricitabine, lamivudine and tenofovir or NNRTI as efavirenz are the less likely to be hepatotoxic and may often be either dosage reduced or substituted.

HAART classification and drug metabolism

In general, the guidelines recommended for patients naive to HAART regimens include a minimum of three active drugs to prevent resistance: a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) with a NNRTIs or a PI boosted with ritonavir or an integrase strand-transfer inhibitor (INSTI). The concomitant use of HAART and AC may be associated with an increased risk of toxicity secondary to pharmacokinetic and pharmacodynamic interactions mediated by drug-metabolizing enzymes or transporters leading to altered drug exposure. For the majority of antiretroviral drugs that are CYP450 substrates, inducers or inhibitors, co-administration with other metabolized drugs could result in drug accumulation and possible toxicity or decreased efficacy of one or both drugs[10]. Particularly, drugs that inhibit CYP450 enzymes generally lead to a decreased metabolism of other drugs metabolized by the same enzyme (Table 1). The decreased metabolism can result in higher drug levels and increased potential of toxicity. Inhibition of CYP450 tends to be rapid, with maximal inhibitory effect occurring when steady-state concentrations of the inhibitor are established. Conversely, induction of CYP450 system results in the increased clearance of concomitant medication metabolized by the same enzyme and a decrease of the drug concentration. Enzyme induction occurs more slowly than inhibition because the full effect of induction is based on the time required for new enzyme synthesis and the half-life of the inducing agent.

Role of Pharmacogenomic associated to HAART

Response to HAART is highly complex and often limited by the development of short- or long-term toxicities and the emergence of antiretroviral drug resistance. This variability can be explained by factors regulating the availability of drugs (pharmacokinetics), effects on the host (host pharmacodynamics), and the activity of the virus itself (viral pharmacodynamics).

The effectiveness of therapy is affected by the viral sensitivity to a drug. Mutagenesis is a constant process in the viral genome; mutations occur at each replication cycle, thereby enabling the virus to easily adapt. Furthermore, initial antiretroviral therapy could be compromised by transmitted HIV drug resistance[11].

Other factors may also contribute to treatment failure: inter-individual variability in the pharmacokinetics of antiretroviral drugs can play a role in treatment failure or toxicity, either directly, because sub therapeutic drug levels can increase the risk of a poor virologic response, or indirectly, when high (toxic) drug levels produce significant intolerability, lead to poor adherence. Variability

Table 1. Polymorphisms influencing the *Pharmacokinetics of HAART.*

Drugs	GENE	SNP (rs code)	Allele	Annotation	Ref.
EFV	CYP2B6	rs3745274	*6	Variants in the CYP2B6 gene have been shown	12
		rs12721655	*8,13	to associate with increased plasma levels of EFV	
		rs35303484	*11	in HIV patients.	
		rs36060847	*12		
		rs35773040	*14		
		rs35979566	*15		
		rs28399499	*16, *18		
	CYP2A6	rs1801272	*2	CYP2A6 may result in extremely high plasma	13
		rs28399433	*9	levels and risk of treatment discontinuation	
NVP	CYP2B6	rs3745274	*6	Predisposed to high plasma levels	13
		rs12721655	*8,*13		
		rs35303484	*11		
		rs36060847	*12		
		rs35773040	*14		
		rs35979566	*15		
		rs28399499	*16,*18		
ETV	CYP2C9	rs1057910	*3	Predisposed to high plasma levels	13
	CYP2C19	rs12571421	*2		
LPV	ABCB1	rsrs1045642	3435T	TT allele is Hepatotoxic Predisposed	16
	ABCC2	rs717620	T	to high plasma levels	
	CYP3A	rs6945984	C		
	SLCO1B1	rs4149056	*5		
		rs17329885	*4	Predisposed to low plasma levels	

Abbreviations: EFV, Efavirenz; NVP nevirapine*; ETV* Etravirine*; LPV, Lopinavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor*; *PI: Phosphatase Inhibitor. Solute Carrier Organic Anion Transporters (SLCO alias OATP).*

between patients in relation to the bioavailability and distribution of antiretroviral drug regimens is probably driven by genetic and environmental factors such as drug-drug interactions, drug-food interactions, sex, and body weight. In particular, drug-drug interactions and genetic polymorphisms in drug-metabolizing enzymes and drug transporters contribute to wide variability in drug pharmacokinetics, response to therapy, and toxicity (Table 1).

The *CYP2B6* gene is highly polymorphic, and more than 28 alleles have been characterized (about 100 SNPs) have. Among different variants, the CYP2B6*6 haplotype (*516 G>T*, and *785 A>G*) leads to reduced catalytic activity and a significant decrease in protein expression. Several studies reported correlations of Nevirapine and Efavirenz with neurotoxicity, in CYP2B6*6 (516G>T) homozygous individuals[12].

Several polymorphisms of the CYP2C19 gene are associated with reduced enzyme activity. In particular, the CYP2C19*2 allele leads to a 681G>A substitution, causing a stop codon splicing. These poor metabolizer patients have a favorable response (in terms of viral suppression) to Nelfinavir exposure[12].

Variability in metabolic CYP3A5 function is largely ascribed to the *CYP3A5*3* mutant allele and, to a lesser extent, to the CYP3A5*6 and CYP3A5*7 variants. The variant CYP3A5*3 allele produces an alternate mRNA splicing, resulting in aberrant protein, because the early form of a stop codon. Haplotype CYP3A5*3 has been associated to important decreased clearance of indinavir and saquinavir[13].

Association to polymorphism in ATP binding Cassette (ABCC) and efficacy to therapy has been found. Since that, drug transporters are viewed as one of the major mechanisms accounting for suboptimal tissue concentrations of antiretroviral agents. Major studies reported an association between the ABCB1 polymorphism (*3435 C>T*) and the overall risk of hepatotoxicity after nevirapine treatment. This genotype-phenotype association has been confirmed by Ritchie et al[14], which has shown that the ABCB1 *3435 TT* allele are less frequent in the patients' group displaying hepatic toxicity than polymorphic *3435CC* allele. However, a pharmacogenetics study[15] including the *C421A* and *G34A* variants, which have been associated in vitro with a decrease in ABCG2 activity, has found no association of these polymorphisms with intracellular accumulations of zidovudine triphosphate and lamivudine triphosphate, but, to date, data for other Nucleosides analogs are lacking the literature.

Recent data suggest an important role in the influx for Solute Carrier Organic Transporters (SLCO alias OATP) family in the pharmacokinetics of antiretroviral agents. In particular, it has been observed that the SLCO1B1 *521T>C* polymorphism is significantly associated with higher plasma concentrations of lopinavir (LPV) in patients homozygous for the mutant allele (*521CC*), it would suggest that the entry of lopinavir into the liver via the SLCO1A2 influx transporter is an important determinant of lopinavir exposure[16].

A recent study in patients receiving atazanavir and indinavir has found a proportion of grade 3 to 4 hyperbilirubinemia equal to 80% among patients homozygous for the UGT1A1*28 allele, 29% in heterozygous patients and 18% among patients homozygous for the wild-type allele.

Even though, the clinical utility of described polymorphisms involved in HAART based-therapy is in part limited by: i) the evidence that Pharmacogenomic testing improves clinical outcomes is still an open question[17]; ii) the cost-effectiveness of the testing being unknown; and iii) the need to find cliical expertise to interpret laboratory results[18,19].

Anticancer treatment and overview of HAART/AC combination and interactions

The therapeutic approach should take into account three fundamental elements: i) histo and cytological nature of the lesion; ii) the assessment of the extension of the tumour growth; iii) the evaluation of the general disease state[20].

The maintenance of dose-schedule and dose-intensity are the primary principals which are thought to contribute to cancer cure. Some studies have shown that intensive AC protocols are feasible in HIV-infected patients and the outcome of HIV-positive patients with Burkitt lymphoma, diffuse large B-cell lymphoma and Hodgkin Lymphoma is similar to that of HIV-negative patients receiving the same AC regimens[21]. The timing of diagnoses of HIV and malignancy may guide the therapeutic decisions. In some cases cancer treatment should take priority over HAART despite the risk associated with stopping HIV treatment[21]. The concomitant use of antiretrovirals and AC might result in either drug accumulation and possible toxicity or decreased efficacy of one or both classes. In fact, many anticancer agents are metabolized by CYP450 whereby DDIs with HAART is high. Nowadays the availability of over 20 approved antiretrovirals permits the development of regimens that minimize the potential for DDIs and improve the compliance with HAART during AC.

Anthracyclines, antimetabolite agents, antitumor antibiotics and platinum undergo non-CYP450 routes of elimination and would be unlikely to be altered by HAART.[22] Camptothecins undergo non enzymatic routes of elimination, are substrates but not inhibitors or inducers of CYP450 and UGT isozymes and, therefore, are likely to be altered by HAART. On the other hand, DDIs can be anticipated with alkylating agents, corticosteroids, epipodophyllotoxins, taxanes, tyrosine-kinase inhibitors and vinca alkaloids.

Vinca alkaloids (Vinblastine, Vincristine, Vinorelbina): the vinca alkaloids remain an important class of AC traditionally associated with the treatment of breast, lung, testicular cancer; is currently (Vinorelbine, Vinblastine) used for the management of AIDS-related KS. Similarly, vinca alkaloids are substrates of CYP3A4 and are vulnerable to PI and NNRTI. The concomitant administration with CYP3A4 inhibitor causes an inhibition of vinca alkaloids metabolism with an increased risk of neurotoxicity and severe myelosuppression. Particularly, interaction between ritonavir/lopinavir and vincristine is responsible of paralytic ileus. In fact, vincristine is transported by P-gp and is metabolized by CYP3A4. Ritonavir is a potent CYP3A4 isoenzyme and P-gp inhibitor. Lopinavir is also a P-gp inhibitor. These PIs might have delayed vincristine elimination. Conversely, CYP3A4 inducers cause a decrease of vinca alkaloids concentrations with decreased efficacy of drugs[10].

Taxanes: several trials have established the efficacy of paclitaxel for the treatment of AIDS-related KS. Concomitant administration of paclitaxel with CYP3A4 inhibitor causes an increase of taxane concentrations with an increase risk of severe myelosuppression and peripheral neuropathy. The CYP3A4 inducers efavirenz and dexamethasone do not have a significant effect on docetaxel exposure. In an in vivo experiment, docetaxel 20 mg/kg IV has been administered in presence and absence of dexamethasone or efavirenz for 4 days, or single dose ketoconazole or ritonavir[23]. The CYP3A4 inducers efavirenz and dexamethasone have not shown any significant effect on docetaxel AUC. However, the CYP3A4 inhibitors ritonavir and ketoconazole have resulted in a 6.9- and 3.1-fold increase in AUC, respectively[24]. Additional risk benefit to CYP2C8*3 in breast cancer have been reported[24].

Epipodophyllotoxins (Etoposide and Tenoposide): these class of AC is used primarily for the management of haematological malignancies. The metabolism is mediated primarily by CYP3A4 pathway therefore inhibition of CYP3A4 pathway may increase the concentrations of epipodophyllotoxins with an increase risk of mucositis, transaminitis and myelosuppression.[10]

Alkylating agents (cyclophosphamide and ifofosfamide): Despite their structural similarity and similar mechanisms of action, important differ-

ences exist in the metabolism of cyclophosphamide and its isomer ifofosfamide. Cyclophosphamide is an alkylating agents used in the management of HD and NHL for patients with HIV and is metabolised by two separate pathways (CYP3A4 and CYP2B6). Induction of CYP2B6 may increase the amount of active metabolite formed; conversely, PI may decrease the efficacy of cyclophosphamide through CYP2B6 inhibition. Induction of CYP3A4 may increase the activation of the drug and may also produce more potentially neurotoxic metabolites[24].

A pharmacokinetic analysis conducted in 29 HIV-positive patients with non-Hodgkin's lymphoma treated with CHOP with and without concurrent indinavir based HAART, have shown a decrease of cyclophosphamide clearance from 70 to 41-46 mL/min/m^2. However, this didn't translate into excessive toxicity[24]. Induction of CYP3A4 may make more drug available for 4-hydroxylation route and may increase efficacy and toxicity of cyclophosphamide. In contrast, ifosfamide is administered as a racemic mixture of its two enantiomeric forms: R and S-ifosfamide through the CYP3A4 pathway[24].

Anthracyclines (Doxorubicin and Daunorubicin) are agents commonly used in the treatment of both AIDS-related NHL and KS. Fortunately, the potential for adverse drug interactions between CYP-pathways and anthracyclines appears to be minimal. Interactions with PIs or NNRTIs and CYP-pathways may decrease the reduction to free radicals, which may decrease both antineoplastic and cytotoxic properties. Enzyme inducers may do the opposite. Two pharmacokinetic analyses have been conducted in HIV-positive patients with non-Hodgkin's lymphoma treated with CHOP (cyclophosphamide, vincristine, doxorubicin and prednisone) with and without concurrent PI-based HAART. The first study in 19 patients has shown that doxorubicin pharmacokinetics has not been affected by concomitant PIs administration, and PIs exposures have not been altered by doxorubicin[26]. The other study in 29 HIV-positive patients also has shown similar clearance rates of doxorubicin when administered with an indinavir-based cART[25].

Antimetabolites (5-Fluorouraxil, Mtotrexate, Gemcitabine, etc.) include several nucleoside analog drugs used in combination with others antineoplastics in carcinomas and NHLs. Fortunately the potential for adverse drug interactions with HAART appears to be minimal, but the clinical trials in this fields are few. Potential toxicity are considered for high exposures to etravirine due to CYP2C9 inhibition, however, close monitoring may be considered[26].

Case series of 21 HIV-positive subjects on cART (7 NRTI only, 6 on PI, 6 on NNRTI and 2 on PI/NNRTI containing regimens) with anal carcinoma who received radiotherapy plus mitomycin C and 5-fluourouracil without need for dose reductions reported a complete response rate of 81%, 62% of patients has remained free of any tumor relapse during additional follow-up (median, 53 months), with no increased risk of HIV progression[27]. Another case series has reported on 5 HIV-positive patients on cART (4 PI, 1 NRTI) with advanced colorectal cancer receiving oxaliplatin, leucovorin and fluourouracil (FOLFOX-4 regimen) without apparent increase in antineoplastic associated toxicity[27].

Others

***Irinotecan*:** (CPT-11), is a DNA topoisomerase I inhibitor with a broad spectrum of activity against solid tumors. The model of angiogenesis bFGF-induced in mouse cornea suggested that Irinotecan is active also in KS HIV-related. Recent data show that lopinavir/ritonavir has a strong effect on the pharmacokinetic profile of CPT-11 when used as monotherapy in HIV-positive patients with advanced KS. Lopinavir/ritonavir reduces the clearance of CPT-11 by 47%; the area under the curve (AUC) of the oxidized metabolite APC by 81%; and inhibits the formation of SN38 glucuronide. This effect resulted in increased availability of CPT-11 and severe toxicity. Conversely, induction of CYP3A4 or glucuronidation may decrease the efficacy of drug[6]. Pharmacogenomics profile UGT1A1 *28 haplotype with homozygous 7 TA repeat, are at high risk for irenotecan-related toxicities with atazanavir, which also inhibits UGT1A1.

Aromatase Inhibitors (Tamoxifen, Letrozoley, exemestrane): the concomitant use of endocrine-based therapies that lack the potential for CYP3A4 induction should be considered. Tamoxifen, a commonly used estrogen antagonist, undergoes extensive hepatic metabolism involving several isoforms of the CYP system. Induction of CYP3A4 by tamoxifen may decrease NNRTIs or PIs concentrations[28]. Conversely inhibition of CYP3A4 isoforms with PIs or NNRTIs may be increase efficacy, risk and severity of tamoxifen-related adverse effects. Several studies have shown that nelfinavir induces cell cycle arrest, endoplasmic reticulum stress, autophagy and apoptosis in cancer cells and may be an effective drug against breast cancer when combined with tamoxifen in patients with no hormone-responsive tumors[29]. Interactions between HAART and aromatase inhibitors are also theoretically feasible. NNRTis may decrease efficacy of drugs, conversely, PIs may increase concentrations and severity of adverse effects of letrozoley and exemestrane[30].

Corticosteroids: corticosteroids are part of combination AC regimens and may be subjects to changes in their pharmacokinetic and pharmacodynamic effects as a result of antiretroviral-mediated modulation of their biotransformation. In particular, dexamethasone and methylprednisolone are vulnerable to interactions with HAART since the CYP3A4 isoform is the main enzyme mediating the metabolism of these drugs. Dexamethasone may decrease concentrations of NNRTIs and PIs. PIs may increase pharmacodynamic effects of corticosteroids when concurrently used. CYP3A4 inducers, on the other hand, may decrease efficacy of these drugs. Therefore it is necessary to hold HAART in patients receiving prolonged dexamethasone or, alternatively, consider the use of non-CYP3A4 inducing corticosteroid or antiretroviral drugs monitoring, if combination is necessary[2].

Erlotinib, a tyrosine kinase inhibitors, approved for the treatment of non-small cell lung and pancreatic cancer, is metabolized by CYP3A4. Inducers or inhibitors of CYP3A4 enzymes such as PIs (e.g., ritonavir) or NNRTIs (e.g., efavirenz) can modify the metabolism and efficacy of the drug[31]. Recent data suggest that to achieve desired drug exposure, the clinically used dose (150 mg daily) of Erlotinib may have to be significantly reduced (25 mg every other day) or increased (300 mg daily), respectively, when ritonavir or efavirenz is coadministered[31].

Imatinib, a specific inhibitor of tyrosine kinase receptor in particular of the proto-oncogene c-kit, used in the treatment of chronic myelogenous leukemia, is also metabolized by the CYP450 system[6].

Sunitinib, an oral multi-targeted tyrosine kinase inhibitor used for the treatment of advanced renal cancer and gastrointestinal stromal tumors (GISTs), is bio-transformed by CYP3A4 in a major pharmacologically active N-desethyl metabolite[6]. The inhibition of proteasomal activity by specific proteasome inhibitors or cross-reactivity of certain PIs with proteasomal enzymes, recently became of interest due of the anti-tumoral properties of these agents.

Recent data show that ***bortezomib*** and nelfinavir induce cell cycle arrest in cervical cancer cells as reflected by marked changes in the expression of cell cycle-regulatory cyclins and ensuing mitochondrial independent apoptosis[32]. Therefore, the combination of ritonavir and bortezomib induces apoptosis and inhibits renal cancer growth synergistically at clinically feasible concentrations[33].

Genotyping panel assay

Several criteria were used to select polymorphisms for pharmacogenomics panel tests (Tables 1 and 2):

A) Searching the most validated genetic variants known to influencing the Pharmacokinetics/pharmacodynamics of HAART and antineoplastic drugs (www.pharmagkb.org); B) reviewing the most recent studies upgrading in clinical research, in particular, trials including pharmacogenomics profile tests; C) issues evaluating the pharmacoeconomic impact of genotyping testing, likely providing answers for policy making in the incorporation of PGx markers into clinical practice.

Early outline evaluation of genotyping costs

Few studies have addressed the cost-effectiveness of pharmacogenomics testing implication in clinical practice[34]. For example van den Akker et al[35] included thiopurine S-methyltransferase (TPMT) genotyping prior to 6-mercaptopurine treatment in paediatric Acute Lymphoblastic Leukaemia (ALL); the mean calculated cost from 4 European countries was € 2100,00 per life-year considering low myelosuppression-related hospitalization; the cost for genotyping of TMPT mutation averaged around €150,00. In another study, early outline of genotyping cost for "home brew" tests (based on Fluorescent allele discrimination Assay), averaged about €20,00 per SNP[36]. The technology platforms needed for detecting the described SNPs are able to address allelic discriminations (detection of DNA mutant between the two alleles). Rational selection of the best method to detect them is dependent from the specifics aims of different laboratories[37].

Furthermore, the major issues to consider for the clinical laboratories (who are responsible for providing PGx services), are: i) the availability of FDA-cleared tests; ii) the current absence of public reimbursement; iii) the need for genotyping accuracy; and iv) the need to find clinical expertise to interpret laboratory data results[18].

CONCLUSIONS

The concomitant use of HAART and AC might result in either drug accumulation and possible toxicity or decreased efficacy of one or both classes. In fact, many AC are metabolized by CYP450 whereby DDIs with HAART is high. All PIs are potent inhibitors of CYP3A which is important in the metabolism of approximately 50% of all drugs. Conversely NNRTIs may induce metabolism and potentially reduce the efficacy of AC. Although, raltegravir has a low potential for DDIs, the presence of viral mutations limits its use as single active agent in a regimen (Table 2). Interactions can also be a result of modification in the activities of glucuronosyltrasferases and of transport proteins[6].

Table 2. Pharmacogenomics panel test for toxicity prevention during HAART/Antiblastic combined therapy.

Antiblastic Drug	Primary metabolism of antiblastics	Reported Interactions HAART	#Pharmaco-genomics annotations	Comments
Vinca alkaloids				
Vincristine, vinblastine and vinorelbine	CYP3A4	Ritonavir and others PIs	Warning for toxicity in CYP3A4*22 poor metabolizer	High vinca levels may have high risk and severity of peripheral neuropathy, and myelosuppression. If possible, consider modifying cART to a non-PI based regimen
Taxanes				
Paclitaxel Docetaxel	CYP2C8>	Caution when unboosted atazanavir is coadministered with drugs that are CYP2C8 substrates with narrow therapeutic indices clinically significant interactions with CYP2C8 substrates are not expected when atazanavir isvboosted with ritonavir	Breast Cancer Patients carrying CYP2C8*3 haplotype are associated to increased risk of neurotoxicity[35]. Polymorphism T274M in Beta Tubulin VI (BTT VI) gene is associated to severe myelosuppression in patient treated to Taxanes[36]	High taxane levels with CYP3A4 inhibitors may have high risk and severity of myelo-suppression, and peripheral neuropathy
Epipodophyllotoxins				
Etoposide Teniposide	CYP3A4 (main); CYP2E1, 1A2 (minor)	Risk of toxicity with all CYP3A4 inhibitors	Warning for toxicity in CYP3A4*22 poor metabolizer	High etoposide/teniposide levels may have high risk and severity of mucositis, myelosuppression and transaminates.
Alkylating agents				
Ciclopho-sphamide	CYP2B6 > 2C19 to active metabolite. 3A4 to inactive and possibly toxic metabolites[2]	CYP2B6 inducers (e.g., ritonavir, nelfinavir, efavirenz, nevirapine) and CYP3A4 inhibitors (e.g., PIs, elvitegravir/ cobicistat.Etravirine inhibits 2C19 Rilpivirine induces CYP2C19; monitor for toxicity	ND	Induction of 2B6 have high amount of active metabolite formed. Inhibition of CYP2B6 may prevent activation of the drug. Induction of 3A4 may have neuro-toxicity, whereas inhibition of 3A4 may make more drug available for 4-hydro-xylation route. Inhibition of 2C19 may impact activation of the drug, although this may be compensated for by increased shunting through 2B6 pathway.
Ifosfamide	CYP3A4 to active metabolite.3A4 and 2B6 involved in detoxification	May need to hold antiretrovirals or change to regimen without CYP3A4 inhibitors		CYP3A4metabolism of (S)-ifosfamide may generate neurotoxic[25]. Induction of 3A4 may produce myelosuppression, arrhythmia, hemorrhagic cystitis
Platin-derivates	Primarly renal elimination post Glutathione additions (GSTP1, GSTM1 and others)	Potential for pharmaco-kinetic interactions with ARVs appears minimal. However, cisplatin induced nephrotoxicity may necessitate dosage adjust-ment for certain ARVs. Potential additive renal toxicity with tenofovir	Polymorphism *GSTP1* rs1695 Ile105Val (313A>G in exon 5, sometimes labelled GSTP1*B) has been associated with reduced enzyme activity and toxicity[37]	Monitor serum creatinine and creatinine clearance; adjust antiretroviral doses accordingly as needed.

Table 2 *(Continued)*. Pharmacogenomics panel test for toxicity prevention during HAART/Antiblastic combined therapy.

Antiblastic Drug	Primary metabolism of antiblastics	Reported Interactions HAART	#Pharmaco-genomics annotations	Comments
Anthracyclines				
Daunorubicin Dactinomycin Doxorubicin	Aldoketoreductase and NADPH-dependent cytochrome reductase. Resulting aglycone derivatives conjugated to a sulfate or glucuronide metabolite. Involved in free radical generation. Substrate of P-gp which may influence intracellular concentrations	Monitor for efficacy and toxicity with concomitant P-gp inhibitors or inducers	Resistance prevention by Detection of MDR1 (ABCB1) 3435C>T	Potential for interactions unknown, given uncertainty about role of CYP450 in free radical generation. P-gp inhibitors may increase intracellular accumulation of doxorubicin, which may enhance cytotoxic effects and/or systemic toxicity
Corticosteroids				
Dexamethasone Prednisone	CYP3A4 Dexamethasone is a 3A4inducer	Dexamethasone may reduce levels of NNRTIs, PIs and elvitegravir/cobicistat[2]	Resistance prevention by Detection 3435C>T. In addition check Vitamin D receptor (VDR) Taq, Apa, BsmI, FokI	Consider use of non-CYP3A4 inducing steroid, or modifying to a non-CYP based cART regimen (e.g., dolutegravir, raltegravir)
Antimetabolites				
Cytarabine	Metabolized in liver byCytidine Deaminase	Caution with AZT; tenofovir due to renal toxicity	CDA haplotype: -451C>T, -92A>G, Lys27Gln results in toxicity[38]	Main toxicities of cytarabineinclude dose-limiting myelosuppression, nausea, vomiting, urinary retention, renal failure (rare).
Fluoropyrimidines	Metabolism by the dihydropyrimidine-dehydrogenase (DPD). 7-20% renally excreted. Strong inhibitor of CYP2C9	Possibile interaction with either CYP2C9 inhibitors (e.g. Efavirenz and Etravirine) or 2C9 Inducer (Elvitegravir)	DPYD*2A haplotype results in severe toxicity[44]	Severe mucosites and gatrintestinal for DPYD deficient
Gemcitabine	Extensively metabolized to 2',2'-difluoro-deoxyuridine (dFdU) by CDA enzyme The main metabolite dFdU has a long terminal half-life after oral administration	Potential for cytochrome-mediated interactions with ARVs appears minimal	Need to asses CDA haplotype: -451C>T, -92A>G, Lys27Gln. In additions check polymorphisma on Nucleotide Trasporters (hENT1)[45].	Unlikely to result in detrimental pharma-cokinetic interactions with cART
Tyrosine Kinase Inhibitors				
Erlotinib	Primarily metabolized by CYP3A4. Metabolized to a lesser extent by CYP1A2 and1A1	Dosing reduction of erlotinib 50 mg daily when coadministering with ritonavir100 mg daily	Erlotinib binding affinity for EGFR exon 19 deletion or exon 21 L858R mutations is higher than its affinity for the wild type receptor	Alternative treatments lacking potent CYP3A4 inducingactivity should be considered when possible
Imatinib	Extensively metabolized by CYP3A4. And N-demethylated piperazine derivative is the main circulating metabolite	Interferences PIs, NNRTIs,and elvitegravir/cobicistat	Consider specific resistance to imatinib due to acquired mutations of ABL gene (i.e T315I)	Monitor patients for signs of imatinib dose-related adverse events (fluid retention/weight gain, nausea and vomiting, neutropenia)
Sunitinib	Metabolized primarily by CYP3A4 to active metaboliteSU012662 which is also meta-bolized by CYP3A4	Avoid concomitant administration of CYP3A4 inhibitors such as PIs and elvitegravir/cobicistat, or inducers such as NNRTIs if possible. Sunitinib dose may be reduced	Patients with metastatic Renal Carcinoma carrying an ABCG2 421 AA genotype developed significantly more grade 3 or grade 4 thrombocytopenia, neutropenia	Potential for high concen-trations with CYP3A4 inhibitors. In healthy volunteers, coadministration of single dose sunitinib and ketoconazole led to 49% high Cmax and 51% high AUC of sunitinib[31]

Table 2 *(Continued)*. Pharmacogenomics panel test for toxicity prevention during HAART/Antiblastic combined therapy.

Antiblastic Drug	Primary metabolism of antiblastics	Reported Interactions HAART	#Pharmaco-genomics annotations	Comments
Miscellaneous				
Irinotecan	hCE2 to SN-38 metabolite (active); CYP3A4 and Glucuronidation by UGT1A1	Potential for augment irenotecan-related toxicities with atazanavir, which also inhibits UGT1A1	Need to detect UGT1A1 *28. Haplotype carrying TA repeat 7/7 is high risk toxicity due poor metabolizer.	Inhibition of 3A4 may have high risk and severity of myelosuppression. Induction of 3A4 or glucuronidation may augment efficacy of drug[6].
Bortezomib	Metabolized primarily byCYP3A4, 2C19, 1A2, and CYP2D6 and CYP2C9 to a minor extent. It may inhibit CYP2C19 at clinically relevant dosages.	Efavirenz and etravirine inhibitCyP2C19 and induce CYP3A4. Clinical significane unknown; monitor for bortezomib efficacy & toxicity. Rilpivirine induces CYP2C19		Potential variation for bortezomib concentrations with potent CYP inhibitors or inducers of CYP3A4 and CyP2C19. monitor for efficacy[32]
Tamoxifene	Multiple isoenzymes involved:CYP3A4> CYP1A2 to N-desmethyltamoxifen. In addition CYP2D6, CYP2C9/19,CYP3A4 and CYP2B6 to trans-4-hydroxytamoxifen may inducer to CYP3A4.	Potential for reduction levels of PIs, NNRTIs orelvitegravir/cobicistat[29]	Genotyping FDA and EMA recomandation guidelines for CYP2D6 *4 Pro34Ser	Inhibition of 3A4 may augment risk and severity of tamoxifen related sideeffects (e.g. hot flushes, nausea and vomiting). Avoid concomitant use of CYP2D6 inhibitors
Exemestrane Letrozole	Metabolized by CYP3A4 and Aldoketoreductases Letrozole is a substrate to CYP2A6 too.	Nevirapine and efavirenz may reduce efficacy. High levels with PIs and delavirdine may augment risk and severity of adverse effects (e.g. hot flashes musculoskeletal pain, peripheral edema, etc.	Genome wide study in breast cancer treated with aromatase inhibitors shown significant polymorphism in TUBB1 rs10485828[36]	Avoid combination to efavirenz and PIs if possible.# referred to Phamacogenomics Knowledge Base www.pharmgkb.com

Available data from www.pharmagkb.org

Ritonavir is an inhibitor of P-glycoprotein which leads to increased expositions towards many antineoplastic drug. Generally, to prevent DDIs and avoid severe toxicity, treatment options include substituting an antiretroviral alternative, or temporarily discontinuing HAART, or selecting an alternative chemotherapy regimen[10]. Zidovudine is associated with severe neutropenia whereby it should not be combined with cytotoxic regimens containing neutropenic agents. Didanosine and stavudine, NRTIs once used, are associated with irreversible peripheral neuropathy, which is also a common side effect of platinating agents, taxanes, vinca alkaloids and bortezomib. Antiblastic chemotherapy induced neuropathy is generally cumulative or dose related, with management consisting of dose-reduction or lower dose intensity. PIs and newer molecularly targeted AC, including the tyrosine kinase inhibitors, may cause QT prolongation, arrhythmias and sudden death. In addition to PIs, it appears to significantly potentiate the myelotoxicity of AC. Bilirubin is often used as a guide for dose adjustment for AC agents such as docetaxel, doxorubicin, etoposide, irinotecan, paclitaxel, sorafenib, vincristine. Several antiretrovirals as atazanavir and indinavir are associated with unconjugated hyperbilirubinemia secondary to UGT1A1 inhibition similar to that occurring in Gilbert's syndrome. If no other signs of liver dysfunction exist, suggested dose modifications of AC based on liver function test may be ignored. For these reasons it is important that patients with cancer should be screening for HIV infection and the treatment of HIV infection should be started immediately[38]. HAART should be individualized according to the cancer treatment plan (AC or radiotherapy or surgery), liver or renal diseases, bone marrow suppression, mitochondrial dysfunction and for individual genetic profile. Finally, anticancer drug metabolism has been described and treatment regimens should be plan calibrating dosage on in-

dividual genomic profile[39]. In the 2, the most important warning of: Taxan[40,41], Platin-derivates[42], Cytarabine[43], Pirymidines[44], Gemcitabine[45], Aromatase inhibitors[30], have been reported.

In the next future, we account that HIV/AC treatment will be formulated in consideration of individual genetic profile of the AIDS patients[46].

Finally, it is fundamental the cooperation between oncologists and laboratory specialist in the management of genetic information related to individual patients profile for decision-making treatments.

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